UNIVERSITI PUTRA MALAYSIA

# *SYNTHESIS OF ZINC-LAYERED HYDROXIDE AND ZINC-ALUMINIUM-LAYERED DOUBLE HYDROXIDE AS HOST OF ULTRAVIOLET RAY ABSORBING MOLECULES FOR SUNSCREEN APPLICATION*

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**ITMA 2014 12**

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By

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**Thesis Submitted to the School of Graduate Studies, Universiti Putra Malaysia, in Fulfilment of the Requirements for the Degree of Master of Science**

**February 2014**

Abstract of thesis presented to the Senate of Universiti Putra Malaysia in fulfilment of the requirement for the degree of Master of Science

# SYNTHESIS OF ZINC-LAYERED HYDROXIDE AND ZINC-ALUMINIUM LAYERED DOUBLE HYDROXIDE AS HOST OF ULTRAVIOLET RAY ABSORBING MOLECULES FOR SUNSCREEN APPLICATION

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**February 2014**

**Chair: Professor Mohd Zobir bin Hussein, PhD**
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New sunscreen formulation was formulated with the intercalation of organic ultraviolet (UV)-ray absorbing molecules into two layered materials; namely zinc layered hydroxide (ZLH) and Zn/Al layered double hydroxide (LDH). Intercalation in inorganic matrix was attempted with the intention of maintaining UV absorption properties of the otherwise photodegradable organic molecules. Furthermore, ZLH and LDH as host carriers provide a barrier between skin and chemical compounds and consequently prevent the phototoxic and photoallergic reactions.

ZLH intercalated with cinnamate (CA) was successfully synthesized using direct reaction of zinc oxide (ZnO) and cinnamic acid. The intercalated compound, ZCA, has a basal spacing of 23.9 Å, with the estimated percentage loading of CA around 40.4 w/w %. The intercalation of benzophenone 9 (B9) into Zn/Al LDH was carried out by two different routes; co-precipitation and ion exchange method. Powder x-ray diffraction (PXRD) patterns of the co-precipitated product (ZB9C) and ion exchanged product (ZB9I) showed basal spacing of 15.9 Å and 16.6 Å, respectively. The percentage loading of B9 anions is 46.6 w/w % for ZB9C and 43.9 w/w % for ZB9I. The intercalation of CA, benzophenone 4 (B4) and eusolex® 232 (EUS) into Zn/Al LDH was also successfully performed via co-precipitation method with the expansion of basal spacing from 8.8 Å in Zn/Al LDH to 17.9 Å, 21.3 Å and 21.0 Å, respectively. Percentages loading of CA, B4 and EUS anions in Zn/Al LDH host are 35.8 w/w %, 41.9 w/w % and 41.7 w/w %, respectively.

Co-precipitation of equimolar concentration of B4 and EUS with Zn/Al LDH host showed an intercalation selectivity that is preferential to EUS. It was also shown that the selectivity ratio of intercalated anions was altered by varying molar ratio of guests during the synthesis. Dual-guest nanocomposite synthesized with B4:EUS molar ratio 3:1 (ZEB (3:1)) showed an intercalation percentage of 20.5 w/w % for B4 and 17.9 w/w % for EUS. The selectivity ratio of B4:EUS could be rephrased as

53:47. ZEB (3:1) nanocomposite was monitored using PXRD and showed a basal spacing of 21.8 Å, which is slightly larger than single intercalation product of B4 and EUS in Zn/Al LDH.

The solid-state absorbance spectra of UV absorbent-intercalated compounds showed broadened UV absorptivity range compared to pure UV absorbent due to the spatial confinement and host-guest interactions. Retention study of sunscreen molecules in ZLH and LDH was conducted with various release media; namely deionized water, pH 5.5 phosphate buffer (skin pH simulation) and 0.5 mol/L NaCl solution (artificial sea water), to observe nanocomposites performance in close to actual application. Anion release patterns in release media showed a slowed and restricted deintercalation from inorganic host.

The cytotoxicity study of intercalation compounds on human dermal fibroblast (HDF) cells was investigated using Methylthiazol Tetrazolium (MTT) assay. In general, 24 h exposure with nanocomposites did not produce any significant cytotoxicity up to maximum concentration of 25 µg/mL.

In brief, the UV absorbent/layered material system show great promise as a safe and efficient sunscreen formulation with prolonged UV protection effect.

Abstrak tesis yang dikemukakan kepada Senat Universiti Putra Malaysia sebagai memenuhi keperluan untuk ijazah Master Sains

# SINTESIS ZINK-HYDROKSIDA BERLAPIS DAN ZINK-ALUMINIUM HIDROKSIDA LAPIS BERGANDA SEBAGAI PERUMAH KEPADA MOLEKUL PENYERAP SINAR ULTRAUNGU UNTUK KEGUNAAN SEBAGAI SEBAGAI PELINDUNG CAHAYA MATAHARI

Oleh

**SUMAIYAH BINTI MEGAT NABIL MOHSIN**

**Februari 2014**

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Formulasi pelindung cahaya matahari baru telah disintesiskan dengan menginterkalasikan molekul-molekul organik penyerap sinar ultraungu (UV) ke dalam dua bahan berlapis; iaitu zink hidroksida berlapis (ZLH) dan Zn/Al hidroksida berlapis ganda (LDH). Interkalasi ke dalam matriks bukan organik telah dilakukan dengan tujuan untuk mengekalkan sifat penyerapan sinar UV molekul-molekul organik yang boleh terfotodegradasi. Tambahan pula, ZLH dan LDH sebagai perumah boleh menjadi penghalang antara kulit dan sebatian kimia, dimana yang demikian dapat mengatasi reaksi fototoksik dan fotoalahan.

ZLH terinterkalasi dengan sinamat (CA) telah berjaya disintesis dengan menggunakan tindak balas secara langsung diantara zink oksida (ZnO) dan asid sinamik. Sebatian terinterkalasi yang diperolehi, ZCA, menunjukkan ruang basal 23.9 Å yang telah dilakukan dengan kajian pembelauan sinar-X (PXRD). Dianggarkan sebanyak 40.4 w/w % CA terinterkalasi. Interkalasi benzofenon 9 (B9) ke dalam Zn/Al LDH telah dilaksanakan melalui dua cara berbeza; iaitu kaedah pemendakan bersama dan kaedah pernukaran ion. Pola PXRD bagi sebatian yang disintesis secara pemendakan bersama (ZB9C) dan secara pernukaran ion (ZB9I) menunjukkan masing-masing mempunyai ruang basal 15.9 Å dan 16.6 Å, hasil daripada pengembangan ruang basal daripada 8.8 Å bagi Zn/Al-$NO_3$ LDH. Peratus kandungan B9 yang direkodkan ialah 46.6 w/w % bagi ZB9C dan 43.9 w/w % bagi ZB9I. Pengembangan ruang basal juga telah berlaku bagi interkalasi CA, benzofenon 4 (B4) dan eusolex® 232 (EUS) ke dalam Zn/Al LDH dengan merekodkan masing-masing 17.9 Å, 21.3 Å dan 21.0 Å. Sebatian terinterkelasi tersebut telah disintesis melalui kaedah pemendakan bersama. Peratus kandungan anion CA, B4 dan EUS di dalam perumah Zn/Al LDH adalah masing-masing 35.8 w/w %, 41.9 w/w % dan 41.7 w/w %.

Kepemendakan B4 dan EUS dengan kepekatan sama ke dalam perumah Zn/Al LDH menunjukkan kepilihan yang memihak kepada EUS. Nisbah kepilihan anion interkalasi berubah dengan mengubah nisbah molar tetamu semasa sintesis. Nanokomposit dwi-tetamu yang telah disintesiskan dengan nisbah molar B4:EUS = 3:1 (ZEB (3:1)) menunjukkan peratus interkalasi sebanyak 20.5 w/w % bagi B4 dan 17.9 w/w % bagi EUS. Nisbah kemilihan B4:EUS ini juga boleh diungkap sebagai 53:47. Nanokomposit ZEB (3:1) telah dipantau menggunakan kaedah analisis PXRD dan menunjukkan ruang basal 21.8 Å, iaitu lebih besar sedikit daripada hasil interkalasi B4 atau EUS ke dalam Zn/Al LDH secara berasingan.

Spektrum penyerapan keadaan pepejal bagi sebatian-sebatian interkalasi penyerap UV menunjukkan julat kebolehserapan yang lebih luas berbanding penyerap UV semata-mata disebabkan oleh pengurungan dalam ruang lapisan dan interaksi antara perumah dan tamu. Kajian pengekalan molekul-molekul penyerap UV dalam ZLH dan LDH telah dijalankan menggunakan media pelepasan; air ternyahion, larutan penimbal fosfat pH 5.5 (simulasi nilai pH kulit) dan larutan 0.5 mol/L NaCl (air laut buatan), untuk mengkaji prestasi nanokomposit dalam keadaan menghampiri penggunaan sebenar. Pola pelepasan anion daripada perumah bukan organik ke dalam media menunjukkan nyahinterkalasi yang perlahan dan terhad.

Kajian kesitotoksikan sebatian terinterkalasi pada sel fibroblast kulit manusia telah diselidik menggunakan ujian Methylthiazol Tetrazolium (MTT). Secara keseluruhannya, pendedahan selama 24 jam kepada nanokomposit tersebut tidak menunjukkan kesiktotosikan yang ketara pada kepekatan sehingga 25 μg/mL.

Kesimpulannya, sistem penyerap UV/bahan berlapis ini menunjukkan potensi besar untuk digunakan sebagai formulasi pelindung cahaya matahari yang selamat dan berkesan.

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I certify that a Thesis Examination Committee has met on 12th February 2014 to conduct the final examination of Sumaiyah binti Megat Nabil Mohsin on her thesis entitled "Synthesis of Zinc-Layered Hydroxide And Zinc Aluminium-Layered Double Hydroxide as Host of Ultraviolet Ray Absorbing Molecules for Sunscreen Application" in accordance with the Universities and University Colleges Act 1971 and the Constitution of the Universiti Putra Malaysia [P.U.(A) 106] 15 March 1998. The Committee recommends that the student be awarded the Master of Science.

Members of the Examination Committee were as follows:

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Date: 21 April 2014

This thesis was submitted to the Senate of Universiti Putra Malaysia and has been accepted as fulfillment of the requirement for the degree of Masters in Science. The members of the Supervisory Committee were as follows:

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Signature: ____________________
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Signature: ____________________
Name of Member of Supervisory Committee: _Taufiq Yap Yun Hin__

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# CHAPTER 1

# INTRODUCTION

## 1.1 Biological effects of exposure to UV radiation

Ultraviolet (UV) radiation is divided into three main groups based on wavelength regions; UVA (320-400 nm), UVB (280-320 nm) and UVC (100-280 nm). The ozone layer functions as an absorber for some of the harmful UV rays. About 90 % of UVB radiation is absorbed by the ozone layer but only 10 % of UVA are absorbed (Jain and Jain, 2010). UVC radiation is of little concern to us as UV rays below 290 nm are mostly absorbed by the ozone layer.

Sunlight is fundamental for the synthesis of vitamin D in skin cells. Nevertheless, prolonged exposure could lead to acute, chronic and delayed effects (Gasparro and Mitchnick, 1998). Examples of acute responses are sunburn and pigmentation. Chronic exposure accelerates photoaging causing dryness, irregular pigmentation, wrinkling (from loss of collagen), actinic keratoses and sebaceous hyperplasia (Gilchrest, 1996). Delayed effects are more frightening as UV radiation has been observed to inflict irreversible damage to cells and DNA. UVB was found to induce direct effect to DNA by forming cyclobutane pyrimidine dimers and 6-4 photoproducts and indirectly by forming highly reactive singlet oxygen species ($O_2^-$) (Griffiths *et al.,* 1998). On the other hand, UVA induces indirect DNA damage through absorption of UVA photons by other cellular structures and forming reactive oxygen species that transfers energy to DNA via mutagenic oxidative intermediates (Dobretsky *et al.,* 1995). Both UVA and UVB cause alterations to p53 tumour suppressor gene, a vital protein that stop the formation of tumours. The connection with solar radiation is evident as 74 % of mutations were found in sun-exposed normal human skin samples and only 5 % were found in unexposed skin samples (Brash *et al.*, 1996).

Due to the rising numbers in skin cancer diagnosed annually, we have to recognize the adverse effects of solar radiation and the need for photo-protection (Jain and Jain, 2010). UV exposure is unavoidable as we go about our daily lives and many physicians believe that the best approach to reduce risk of skin cancer development is by applying sunscreen regularly.

## 1.2 Inorganic layered materials as sunscreen carrier

As with the use of any other chemical compounds on the human body, attention has to be paid over the efficacy and safety of long term and frequent use of sunscreens. Adverse effects of active ingredients in sunscreen formulations have been reported for allergy and photoallergy (Hughes and Stone, 2007; Brancaccio and Alvarez, 2004; Bickers *et al.,* 2005), production of carcinogenic reactive oxygen species (Zhang *et al.,* 2008; Vilela *et al.,* 2012; Bolton *et al.*, 1992) and estrogenic and nonestrogenic activites (Suzuki *et al.,* 2005; Hayashi *et al.*, 2006; Seidlová-Wuttke *et* *al.*, 2004). Yet, sunscreens remain the best form of protection from the sun. A vehicle in which sunscreen molecules are carried in can be utilized to improve efficacy and reduce toxicity of the sunscreen agents.

Considerable research efforts have been undertaken to develop an efficient sunscreen vehicle. The key requirements for an effective sunscreen carrier include; able to retain sunscreen compound on stratum corneum layer of skin and avoid systemic absorption, has high photochemical stability, provide a barrier from skin to avoid photoallergy and phototoxic reactions and easily masked physico-chemical features to allow vast possibility of formulations.

Various natural and synthetic materials have been proposed as sunscreen encapsulation vehicle. These include the use of cyclodextrins (Scalia *et al.* 2004; Berbicz *et al.*, 2011; Simeoni *et al.*, 2004), polymeric microparticles (Gomaa *et al.*, 2010; Patel *et al.*, 2006), solid lipid microparticles (Tursilli *et al.*, 2007, Mestres, *et al.*, 2010) and inorganic layered materials (Cursino *et al.*, 2010, Perioli *et al.*, 2008). Amongst these, inorganic layered material/sunscreen system is predicted to have high possibility for scaled-up manufacture due to its simplicity in synthesizing technology, low cost of raw materials and low toxicity (Blasi *et al.*, 2011).

Inorganic layered materials such as layered double hydroxide salt (LHS) and layered double hydroxide (LDH) has long been the subject of interest as drug, herbicides, polymers, vitamins and UV absorbent carriers. They are built by the stacking of lamellar units connected to each other through electrostatic forces between positively charged lamellar units and charge balancing anions. The lamellar unit itself comprises of covalent bonding of metal cations and hydroxides. Versatility of the layered compounds is due to the structure that is able to retain anionic species of various sized as they expand and contract along the basal axis.

Cursino *et al.* reported the intercalation of several different anionic UV ray absorbers into zinc hydroxide nitrate using the co-precipitation method. The nanocomposites showed an enhanced absorption range of their precursor due to the inheritance on UV absorbing properties of its guest (Cursino *et al.*, 2011). A similar observation was also noted for encapsulation of various organic UV absorbers in Zn/Al LDH host (He *et al.*, 2004). Moreover, encapsulation of sunscreen molecules in LDH and LHS has the ability to restrain formation of active oxygen radicals (Khan *et al.*, 2011; He *et al.*, 2004). Oxidation catalytic activity of organic UV absorbent molecules was reportedly suppressed due to restraint from metal hydroxide layer.

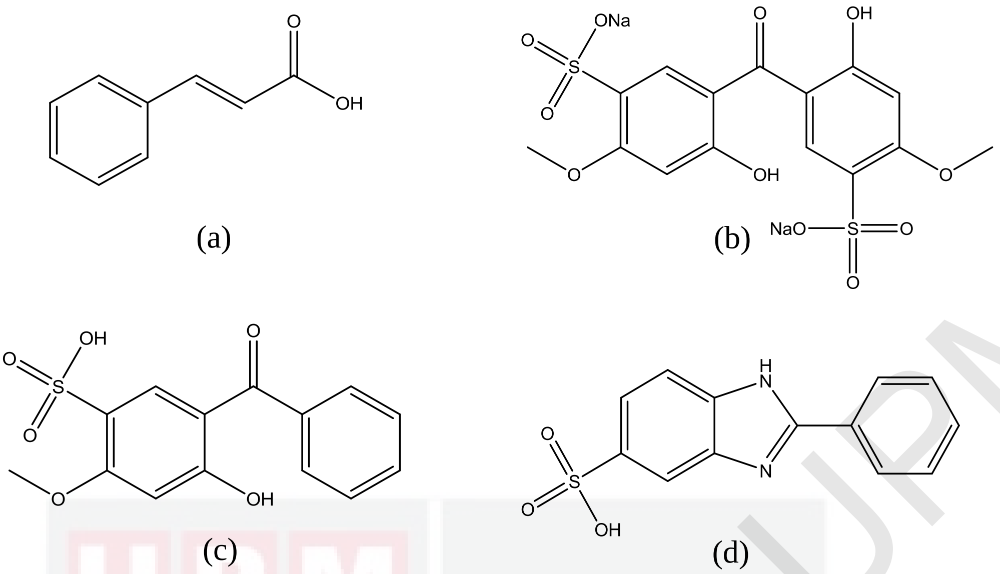
### 1.3 Problem statement

The use of sunscreen products has been advocated by health practitioners as a way to curb excessive UV exposure. As they are becoming widespread and easily attainable, concerns have been raised regarding its long term usage. Sunscreen agents are divided into two types; inorganic and organic. The former act by reflecting or scattering UV radiation, while the latter act by absorbing the radiation and subsequently decreasing the dose of UV rays reaching the skin (Gasparro *et al.*, 1998).

They are two inorganic sunscreen agents; titanium dioxide ($TiO_2$) and zinc oxide (ZnO) nanoparticles. Both UV filters carry a strong capability to absorb UV radiation in a broad spectrum. A study done by Popov *et al.* established that $TiO_2$ and ZnO in nanoscale size provide similar effect in blocking UV radiation to normal-scale sunscreen particles (Popov *et al.*, 2005). Nanosized particles give a more aesthetically pleasing transparent appearance upon topical application, unlike the white residue left on skin by larger sized particles. However due to the size, $TiO_2$ and ZnO nanoparticles pose adverse effects to us as they easily penetrate beyond stratum corneum via hair follicle and remain deep in the epidermis (Tran and Salmon, 2010). *In vitro* assessment of $TiO_2$ and ZnO demonstrated that the nano-scale size significantly contribute to the substantial toxic effect to human dermal fibroblast cells after 24 h exposure (Dechsakulthorn *et al.*, 2007). Even more damaging is that $TiO_2$ and ZnO nanoparticles are susceptible to excitation by UVA and UVB in sunlight and artificial light to generate reactive oxygen species upon radiation and causes photo-induced damage to supercoiled plasmids and human fibroblasts (Shukla *et al.*, 2011; Ng *et al.*, 2011; Baek *et al.*, 2011).

Organic UV absorbers on the other hand are unstable and degrade upon exposure to sunlight. This is followed by a reduction of the protective effect of sun-care product. Furthermore, their degradation is often accompanied with the occurrence of toxic degradation products. Consequently, for longer periods of sun exposure doses of these compounds have to be increased. Ultimately, higher concentration of organic UV absorbers will induce photoallergy and phototoxic reactions in sensitive users.

Figure 1.1 shows the molecular structures of cinnamic acid (a), benzophenone 9 (b), benzophenone 4 (c) and eusolex®232 (d). These organic compounds are commonly used as sunscreen materials due to their excellent UV absorption capability. They bear at least one benzenic moiety and experiences conjugation with electron accepting and electron releasing groups in either *ortho* or *para* position. The electronic delocalization property that they possesses, gives them a specific maximum absorbance wavelength (Santos *et al.*, 2012). Individually, they offer narrow UV ray shielding region. Therefore, they are normally used in combinations with other organic sunscreen to provide broader absorption spectrum.



(a) (b)

(c) (d)

**Figure 1.1. Molecular structure of cinnamic acid (a), benzophenone 9 (b), benzophenone 4 (c) and Eusolex®232 (d).**

In addition to being an efficient UV ray absorber, cinnamic acid (3-phenyl-2-propenoic acid) also possesses antibiotic, antibacterial, antifungal and antiparasitic properties (Park *et al.*, 2010; Kalinowska *et al.*, 2011). Dermatological assessment of cinnamic acid has identified it to be a skin irritant and a major allergen in Balsam of Peru, a resin used as flavouring and fragrance in many products (Bickers *et al.*, 2005; Brancaccio and Alvarez, 2004).

Benzophenones 4 and benzophenone 9 comes from a family of chemical UV filter with a broad absorption range. Benzophenones are known to have both UVA and UVB absorption capability and thus frequently used in cosmetics and toiletries. Recent studies have shown that benzophenones induce adverse effects to human skin upon photo-irradiation (Suzuki *et al.*, 2005). Its parent, benzophenone, undergo metabolic and photochemical activation upon UV or sunlight radiation to produce two estrogenic products that can generate hydroxyl radicals even without UV irradiation (Hayashi *et al.*, 2006). Benzophenone 4 (2-hydroxy-4-methoxybenzophenone-5-sulphonic acid) was found to induce cosmetic dermatitis on face and neck and sensitization at other parts of the body (Hughes and Stone, 2007). Bolton *et al.* reported that benzophenone 9 (disodium 2,2'-dihydroxy-4,4'-dimethoxy-5,5'-disulfobenzophenone) is potentially carcinogenic due to its ability to photosensitize thymine dimer (Bolton *et al.*, 1992).

2-phenylbenzimidazole-5-sulfonic acid or better known by its commercial name, eusolex®232, is a widely popular sunscreen agent because it is water-soluble and thus leaves a non oily finish upon application. Several scientific literatures have reported that solar irradiation of eusolex®232 generates a variety of free radicals and reactive oxygen species (Inbaraj *et al.*, 2002; Bastien *et al.*, 2010; Zhang *et al.*, 2010). Serpone *et al.* reported that photodegradation of eusolex®232 is particularly fast and extensive in aqueous solution and is followed by decrease of UV protection ability (Serpone *et al.*, 2002).

This work is aimed at exploring the potential of LDH and LHS, specifically, zinc layered hydroxide (ZLH) as the carrier for anions of sunscreen agents; cinnamic acid, benzophenone 9, benzophenone 4 and eusolex®232, to be applied in sunscreen formulation.

## 1.4 Objectives of research

The objectives of this study are as stated below:

a) To synthesize cinnamate-ZLH intercalation compound using direct method
b) To synthesize benzophenone 9-intercalated zinc-aluminium-LDH nanocomposites using co-precipitation and ion exchange method
c) To synthesize cinnamic acid-, benzophenone 4- and eusolex®232-intercalated zinc-aluminium-LDH nanocomposites using co-precipitation method
d) To determine selective intercalation of benzophenone 4 and eusolex®232 into zinc-aluminium-LDH using co-precipitation method
e) To determine the physico-chemical properties, UV-absorbing properties, anion retention ability and cytotoxicity of the resulting intercalation compounds.

## 1.5 Thesis overview

Chapter 1 starts with a brief review of the damaging effects of UVA and UVB as well as sunscreen as a method of protection from solar radiation and its limitations. Aim and objectives of the present study are also presented.

Chapter 2 observes the history of cationic clay. This chapter continues with a thorough literature review on the structure, composition, and preparation methods of LDH and LHS. Potential applications of cationic clay in various fields were also discussed. Chapter 2 also briefly touches on selective intercalation, sustained release and cytotoxicity assay of LDHs and LHSs in previous studies.

Chapter 3 is intended to provide a description of experimental design of the present study. Reagents and suppliers and experimental methods followed, as well as analytical instruments used to carry out the characterization of nanocomposites were described in Chapter 3.

Chapter 4 described intercalation study of ZLH with cinnamate, an anionic form of cinnamic acid using direct reaction between anion solution and ZnO. The chapter details physico-chemical properties obtained from the elemental analysis, thermal analysis and morphological analysis. The UVA and UVB absorption ability, retention ability and cytotoxicity of resulting material were also examined and discussed in this chapter.

Chapter 5 presents the results from intercalation of benzophenone 9 into Zn/Al LDH by two different routes; co-precipitation and ion exchange method. The effect of different synthesis methods on physico-chemical properties, UV ray absorption properties, stability of sunscreen molecules in LDH interlayer space and cytotoxicity of the nanocomposites were discussed.

In Chapter 6 we looked into individual intercalation of cinnamic acid, benzophenone 4 and eusolex®232 into Zn/Al LDH as host. The intercalated compounds were prepared via co-precipitation method. Physico-chemical properties, UV-vis absorption properties, retention ability of sunscreen molecules in LDH interlayer space and cytotoxicity of each nanocomposites was investigated and thoroughly discussed.

The potential of layered metal hydroxides as UV absorbent host was ventured further with simultaneous intercalation study of benzophenone 4 and eusolex®232 in Zn/Al LDH in Chapter 7. Initial synthesis using equimolar concentration of both guests via co-precipitation method showed an intercalation selectivity that is preferential to EUS. We then attempted to alter the selectivity ratio of intercalated anions by varying molar ratio of intended guests during synthesis and found it to be successful.

Finally, the summary of whole work is presented in Chapter 8. We discussed the limitations of our work and provided recommendations for future works regarding the use of LHS and LDH as host of sunscreen molecules.

## 1.6 Significance of study

By intercalating UV absorbers into interlayer galleries of ZLH and LDH the expected advantages are (Hoyo, 2007):

a) UV absorber stabilization in the interlayer region of lamellar host
b) maintained absorption of solar radiation in UVA and UVB regions
c) absence of close contact between skin and UV absorbers with the consequent elimination of allergic and unwanted reactions

Compared to pharmaceutical applications, little investment is focused on the cosmetic field and unfortunately, this includes sunscreen products. This leaves very little funding for the development of novel and expensive technologies for sunscreen formulations. However, synthetic clay draws a different story. Low cost of the raw materials, low toxicity potential and the relatively simple synthesis method makes it a probable venture. Therefore we could foresee scale up production and commercialization of inorganic layered clay/sunscreen formulation in the near future.

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