INFLAMMATION: THE KEY TO HEALTH AND DISEASE

Prakash Nagarkatti Ph. D.* and Donald J. DiPette M. D.

University of South Carolina School of Medicine, Columbia, SC

*Dr. Prakash Nagarkatti, Associate Dean for Basic Sciences, Health Sciences Distinguished Professor, Department of Pathology, Microbiology and Immunology, University of South Carolina School of Medicine pnagark@gw.med.sc.edu

INTRODUCTION

Recently, National Institutes of Health (NIH) awarded a 5 year $ 6 million grant to the University of South Carolina (USC) to establish a Center of Excellence for Complementary and Alternative Medicine Research on Autoimmune and Inflammatory Disease. The University of California Los Angeles and the Mount Sinai School of Medicine were the only other institutions awarded centers in 2007. Previously centers have been awarded at Harvard Medical School, Massachusetts General Hospital, Oregon State and Temple universities, and the universities of Maryland, North Carolina and California-San Francisco. The underlying focus of the NIH Center at USC is to study the mechanisms by which plant products suppress inflammation so that they can be used as preventive or therapeutic modalities against autoimmune diseases (http://camcenter.med.sc.edu/). The goal of this review is to provide an understanding of inflammation, discuss its role in health and disease, and provide an overview of how the NIH Center award and research in inflammation at the USC School of Medicine (SOM) provides the niche to bring together many research focus areas in basic and clinical sciences by providing a platform for multidisciplinary collaborations and research advancement.

Inflammation which is defined clinically as heat, pain, redness, and edema, actually results from a physiological response to tissue injury and infection (Oke and Tracey, 2007). Inflammation is a double-edged sword—while it is critical in restoring tissue homeostasis following damage secondary to invading pathogens, foreign bodies, and trauma, inflammation can also trigger acute and chronic diseases. This list includes major pathological disorders such as autoimmune diseases, allergies, cardiovascular diseases, neurodegenerative diseases and cancer. Thus, inflammation plays a critical role in the pathogenesis of a wide range of diseases.

Inflammation can be classified as either acute or chronic. During acute inflammation, the body responds to harmful stimuli through movement of plasma and the white blood cells of the immune system, called leukocytes, from the blood into the injured tissues. Acute inflammation plays a critical role in clearing infections and in tissue healing. If the inflammation persists for prolonged periods, it is known as chronic inflammation. This can lead to a progressive shift in the nature of immune cells that are present at the site of inflammation and can trigger tissue destruction, injury and organ failure. During inflammation, the cells of the immune system release a large number of chemical mediators known as chemokines and cytokines. Some of the important cytokine mediators include interleukin (IL)-1, IL-6, tumor necrosis factor (TNF), and interferon gamma (IFN). In the early stages of inflammation, the predominant cell type infiltrating the tissues is the neutrophil. In contrast, accumulation and activation of

macrophages is the hall mark of chronic inflammation. In addition, lymphocytes also contribute towards the development of inflammation by producing cytokines and chemokines.

Autoimmune diseases are disorders in which the immune system, for reasons that are not clear, starts destroying an individuals own cells, tissues or organs by triggering inflammation. These diseases include more than 80 serious, chronic illnesses that involve almost every human organ system. Collectively, they affect 15-20 million people in the USA. They are more common in women and are considered to be among the 10 leading causes of death in women in the US under the age of 65 years. Currently, there is no known cure for autoimmune diseases. Prominent examples of these diseases include Coeliac disease, diabetes mellitus type 1 (IDDM), systemic lupus erythematosus (SLE), Sjögren's syndrome, multiple sclerosis (MS), Hashimoto's thyroiditis, Graves' disease, idiopathic thrombocytopenic purpura, myesthenia gravis and rheumatoid arthritis (RA).

The main objective of newly funded NIH Center at USC is to conduct research that would determine whether various plant-derived compounds possess immunosuppressive activity and to determine their efficacy against autoimmune diseases. Initially, the NIH Center will pursue three projects. Project one, led by Dr. Prakash Nagarkatti from the USC SOM, will investigate the effect of resveratrol (trans-3,5,4'-trihydroxystilbene) on experimental allergic encephalomyelitis (EAE), a model for human MS. Resveratrol, a polyphenolic compound found in plant products including red grapes, exhibits anticancer, antioxidant, and anti-inflammatory properties. Recently, we demonstrated that resveratrol treatment decreased the clinical symptoms and inflammatory responses in an experimental MS model (Singh *et al.,* 2007). Resveratrol was shown to act through the Aryl Hydrocarbon receptor (AhR) and estrogen receptors (ER) found on immune cells which, in turn, triggered apoptosis (programmed cell death) in these cells. Resveratrol administration also led to significant down-regulation of certain cytokines and chemokines including TNF-alpha, interferon-gamma, and the interleukins (IL)-2, IL-9, IL-12, IL-17, for instance (Singh *et al.,* 2007). These studies suggest that resveratrol and other plant-derived products may be benefiscial in the treatment of not only autoimmune diseases but also other inflammatory disorders as well. Project two, led by Dr. Mitzi Nagarkatti, will investigate the effect of compounds isolated from hemp oil on the suppression of the immune response which may be beneficial in the treatment of autoimmune hepatitis. Project three, led by Dr. Lorne Hofseth from the USC College of Pharmacy will test the efficacy of American ginseng on colitis and colon cancer. Preliminary studies suggest that ginseng is very effective in suppressing colitis and development of colon cancer in an experimental model. The Center will also provide core resource facilities, which will enable, the screening of the potential toxic effects of plant-derived compounds on the immune system. These facilities will be led by Drs Narendra Singh and Robert Price from the USC SOM. The Center will also create training opportunities for new investigators to pursue research on CAM and establish the basis upon which to initiate clinical trials on compounds that exhibit efficacy against specific autoimmune diseases.

While the USC School of Medicine has many areas of research strengths, three specific research areas have been identified for further development. These areas include cancer, cardiovascular diseases and neuroscience. It is interesting to note that

inflammation is a common thread that weaves throughout the pathogenesis of diseases represented in these areas.

INFLAMMATION AND CANCER

Although inflammation is a necessary response to clear infections and to repair tissue injury, chronic inflammation has been shown to correlate an increased risk of developing cancer. Recent studies have revealed that inflammation is a critical component of tumor progression (Coussens and Werb, 2002). Inflammation functions at all three stages of tumor development: initiation, progression and metastasis. Inflammation contributes to the initiation of cancer by triggering the release of a variety of cytokines and chemokines which in turn cause oxidative damage, DNA mutations, and other changes in the microenvironment. Such changes make it more conducive for cell transformation and the increased survival and proliferation of tumor cells. Such novel insights are leading to the use of anti-inflammatory agents as therapeutic approaches to prevent cancer development and progression. The recognition of the importance of inflammation to oncogenesis has led to clinical trials investigating the use of anti-inflammatory drugs, such as COX-2 specific inhibitors for cancer prophylaxis and treatment. A NIH think tank on cancer biology has recently dealt with this topic at length (http://dcb.nci.nih.gov/thinktank/Executive_Summary_of_Inflammation_and_Cancer_Think_Tank.cfm).

CARDIOVASCULAR DISEASES AND INFLAMMATION

It is becoming increasingly clear that inflammation of blood vessels is one of the major factors that increase the incidence of cardiovascular diseases, including atherosclerosis, hypertension, stroke and myocardial infarction or heart attack. Initiation and progression of vascular inflammation is a complex process involving macrophages of the immune system. The proinflammatory mediators produced by macrophages increase tissue oxidative stress and lipid retention, which participate directly in vascular remodeling (Yan and Hansson, 2007). Normally, endothelial cells (ECs), which line the blood vessel, resist adhesion by leukocytes. However, triggers of atherosclerosis, such as consuming a high-saturated-fat diet, smoking, hypertension, hyperglycemia, obesity, or insulin resistance, can initiate the expression of adhesion molecules by ECs, thus allowing the attachment of leukocytes to the arterial wall (Libby, 2006). After adhering to the endothelium, blood monocytes penetrate the endothelial lining and mature into macrophages, and engulf modified lipoproteins. Cholesterol esters accumulate in the cytoplasm, and the macrophages become foam cells through lipid uptake which characterizes the early stages of atherosclerosis. Also, the macrophages multiply and release several growth factors and cytokines, thereby amplifying and sustaining proinflammatory mediators (Libby, 2006). Thus, inflammation is central to the progression from fatty streak to complex plaque. Recent studies suggest that drugs commonly prescribed to lower cholesterol such as statins also reduce inflammation, suggesting an additional beneficial effect of such drugs.

Similar inflammatory tissue processes are also involved in the pathogenesis of hypertension. It is becoming increasingly clear that known mediators that increase blood pressure, such as angiotensin-II, also increase oxidative stress and inflammation both of which contributes to the target organ damage to the heart, brain, kidney, and blood vessels secondary to the hypertensive process. Our laboratory has recently demonstrated

that certain endogenous neuropeptides, such as calcitonin gene-related peptide, improve hypertension by vasodilation and inhibiting oxidative stress and inflammation (Bowers et al., 2005). These studies provide an opportunity for the development of new pharmacologic targets to treat hypertension and its deadly consequences.

INFLAMMATION AND NEURODEGENERATIVE DISEASES:

There is growing evidence that links immune system and the CNS. For example, various immune cells can traverse the blood-brain barrier. During the development of the CNS, blood monocytes populate the brain to differentiate into microglia. Invading lymphocytes can attack target antigens in the CNS such as during MS or produce growth factors that might protect neurons against degeneration. Immune molecules, such as interleukins and chemokines, are also expressed at high levels in neurons and may be involved in the communication of neurons with glial cells. Moreover, the inflammatory reflex is a neurophysiological mechanism that regulates the immune system (Oke and Tracey, 2007). The efferent branch of the reflex include the cholinergic anti-inflammatory pathway involving the vagus nerve, which inhibits inflammation by suppressing cytokine synthesis through the release of acetylcholine in immune organs, the liver, and the gastrointestinal tract. Thus, such a neurological control mechanism regulates inflammation via acetylcholine and suppresses production of proinflammatory cytokines (Oke and Tracey, 2007).

Inflammation during neurodegenerative disorders can be triggered by a number of causes including protein aggregates, molecules released from or associated with injured neurons or synapses, and dysregulation in the mechanisms that control inflammation. The resulting inflammatory responses may modulate neurodegenerative pathways with a potential beneficial or detrimental effect. Emerging evidence suggests that inflammation may account for chronic neurodegenerative diseases such as Alzheimer's disease (AD), Parkinson's disease (PD) and Creutzfeldt–Jakob disease (Minghetti, 2005). In these diseases, inflammation is atypical and occurs in the absence of robust leucocyte infiltration. In these diseases, resident microglia which are the macrophages of brain parenchyma appear to play a major role. In healthy normal brain, microglia are present in an inactive phase as compared with other tissue macrophages, but subtle microenvironmental changes can induce microglia to react rapidly, change morphology and acquire an array of functions, including phagocytosis and secretion of inflammatory mediators. In addition to microglia, reactive astrocytes contribute to the process by restricting the area of lesion and releasing local mediators. This localized process, is distinct from inflammation seen in other tissues and is often referred to as 'neuroinflammation' (Minghetti, 2005). This unique neuroinflammation is a double-edged sword which is both neuroprotective as well as can trigger neurodegenerative disorders (Minghetti, 2005). Thus, understanding the dynamic relationship between beneficial and detrimental effects of neuroinflammation is central to the prevention and treatment of neurodegenerative diseases.

TREATMENT OF INFLAMMATION

Historically, anti-inflammatory drugs were discovered when certain plants and their extracts were found to relieve pain, fever and inflammation (Rainsford, 2007). Salicylates were discovered in the mid-19th century from Willow and this enabled the synthesis of acetyl-salicylic acid leading to development of Aspirin. Subsequent research in 19th-

20th centuries led to the development of the non-steroidal anti-inflammatory drugs (NSAIDs), most of which were initially organic acids, but later non-acidic compounds were developed. The major adverse effects associated with NSAIDS were the associated gastro-intestinal (GI) toxicity. In the 1990's two cyclo-oxygenase (COX) enzyme systems controlling the production of prostaglandins (PGs) and thromboxane (TxA2) were discovered. COX-1 produces PGs and TxA2 which play a role in gastrointestinal, renal, and vascular functions, and COX-2 produces PGs which are involved in inflammation, pain and fever. This led to the discovery of inhibitors of the COX enzymes. While COX-2 inhibitors were enthusiastically received due to their low GI side effects, there are recent concerns regarding an increase in cardiovascular toxicity of these agents. Because inflammation plays a crucial role in the pathogenesis of a wide range of diseases including autoimmune diseases, allergies, cancer, cardiovascular diseases and neurodegenerative diseases as discussed above, one can imagine how crucial it is to discover new anti-inflammatory drugs, and the potential impact such discoveries will have on human health and disease.

CONCLUDING REMARKS :

Inflammation is a process that enables the host to fight and overcome infections, cancer and help repair damaged tissues. Interestingly, however, inflammation has become one of the hottest areas of medical research because it also plays a significant role in the pathogenesis of a large number of human diseases, including autoimmune diseases, allergies, cardiovascular diseases, neurodegenerative diseases and cancer. It is indeed distressing that despite extensive research, highly effective treatment modalities do not exist to treat inflammation. The concept that inflammation contributes to the underlying cause of such varied diseases is so intriguing because it suggests the possibility to treat major human ailments through a single inflammation-reducing agent. Thus, it is not surprising that the NIH in its new roadmap initiatives for 2008 has identified inflammation as one of the key topics. The NIH website (http://nihroadmap.nih.gov/2008initiatives.asp) states, "While significant breakthroughs have occurred in our understanding of inflammation, research is needed to further understand inflammatory processes. Because inflammation is broadly implicated in many diseases and conditions, this initiative would be valuable in uncovering as-yet-unknown immune mechanisms and mediators of inflammation as well as genetic factors, environmental triggers, and the relationship of inflammation to disease".

The USC SOM is excited about the recognition of its research efforts afforded by the NIH to initiate and develop the Center for Autoimmune and Inflammatory diseases with the research focus on inflammation, and we believe that this initiative provides us with the niche not only to advance research on inflammation but also extend it to other areas of research including cancer, cardiovascular diseases and neurodegenerative disorder.

LITERATURE CITED

Bowers, M, Katki, K, Rao, A, Koehler, M, Patel, P, Spiekerman, A, DiPette, D.J, Supowit, S.C. Role of Calcitonin Gene-Related Peptide in Hypertension-Induced Renal Damage. Hypertension , 45:109-114, 2005.

Coussens, L. M. and Werb, Z. Inflammation and cancer. Nature, 420: 860-867, 2002.

Libby, P. Inflammation and cardiovascular disease mechanisms. American Journal of Clinical Nutrition, 83: 456S-460S, 2006.

Minghetti, L. Role of inflammation in neurodegenerative diseases. Curr Opin Neurol, 18: 315-321, 2005.

Oke, S. L. and Tracey, K. J. From CNI-1493 to the immunological homunculus: physiology of the inflammatory reflex. J Leukoc Biol, 2007.Rainsford, K. D. Anti-inflammatory drugs in the 21st century. Subcell Biochem, 42: 3-27, 2007.

Singh, N. P., Hegde, V. L., Hofseth, L. J., Nagarkatti, M., and Nagarkatti, P. Resveratrol (trans-3,5,4'-trihydroxystilbene) ameliorates experimental allergic encephalomyelitis, primarily via induction of apoptosis in T cells involving activation of aryl hydrocarbon receptor and estrogen receptor. Mol Pharmacol, 72: 1508-1521, 2007.

Yan ZQ, Hansson GK. 2007. Innate immunity, macrophage activation, and atherosclerosis. Immunology Review. 219: 187-203.

POLYMER-LAYERED OXIDE NANOCOMPOSITES

Tara J. Hansen and Hans-Conrad zur Loye

Department of Chemistry and Biochemistry, University of South Carolina, Columbia, SC1.1.

POLYMER NANOCOMPOSITES

Polymer nanocomposites are composite materials that consist of nanoscale additives dispersed in a polymer matrix where, typically, a layered material capable of exfoliation into nano-sized platelets is incorporated into the polymer. Since the composites are mixed on the nanometer length scale, they often exhibit enhanced properties compared to their macroscale counterparts, such as improved strength, stiffness, thermal stability, biodegradability, flame resistance, and gas barrier (Schmidt *et al.* 2002). Types of polymer matrices studied include, but are not limited to, vinyl polymers (polymethacrylate, polystyrene), condensation polymers (Nylon, polyethylene terephthalate), polyolefins (polypropylene, polyethylene), epoxides, rubber, and other specialty polymers such as polypyrrole and polyaniline (Ray and Okamoto 2003). Additives that are potential candidates for polymer nanocomposites include natural, commercial, and synthetic clays, layered silicic acids, layered hydroxides, layered double hydroxides, layered alumino-phosphonates and other metal oxides (Utracki *et al.* 2007). However, the vast majority of nanocomposite research is directed towards polymer matrices containing layered silicate platelets of nanometer thickness and high aspect ratio and these types of nanocomposites will be highlighted in later sections.

Nanocomposite materials are useful in a wide variety of applications in medical, automotive, fiber, textile, coatings, electronics, and packaging industries, among others. Research in this area has increased substantially after a Toyota research team developed one of the first successful montmorillonite–Nylon-6 nanocomposites in an effort to use Nylon-6 based parts in engine compartments and for automotive applications (Kojima *et al.* 1993, Usuki *et al.* 1993). Since then, layered-oxides, specifically layered silicates, have attracted a great interest as additives (Schmidt *et al.* 2002, Ray and Okamoto 2003, Kojima *et al.* 1993, Usuki *et al.* 1993, Alexandre *et al.* 2002, Alexandre and Dubois 2000, Bharadwaj *et al.* 2002, Carrado 2003, Chang *et al.* 2003, Chang and Yeong 2002, Dai and Huang 1999, Fornes *et al.* 2002, Garces *et al.* 2000, Gilman *et al.* 2000, Gopakumar *et al.* 2002, Grunlan *et al.* 2004, Hoffman *et al.* 2000, Imai *et al.* 2003, Jan and Lee 2004, Jordan *et al.* 2005, Matayabas *et al.* 2000, Pinnavaia and Beall 2000, Sekelik *et al.* 1999, Strawhecker and Manias 2000, Kim and Kim 2007, LeBaron *et al.* 1999, Tsai 2000).

Researchers at Eastman Chemical Company expanded on the work of Toyota, by incorporating montmorillonite, ion-exchanged with alkylammonium compounds, into polyethylene terephthalate (PET) via melt-blending and in-situ polymerization (Matayabas *et al.* 2000a, Matayabas *et al.* 2000b). They found that at even a low weight loading of montmorillonite clay, the oxygen permeability decreased dramatically. This was an important finding for Eastman, a leading producer of PET, as their motivation was to increase the gas barrier of PET for use in food and beverage packaging. Although research in polyester-clay nanocomposites is in a relatively early stage, over 28 patents for PET-clay nanocomposites were issued between the years of 1991 and 1998, suggesting that this a thriving area of research (Tsai 2000). Earlier methods of

incorporating montmorillonite clay into PET were usually based on melt-blending, or melt-intercalation by extrusion. Typically these method do not facilitate full exfoliation of the clay layers but, nonetheless, there were some successful well-exfoliated nanocomposites produced where exfoliation and enhancement in properties were achieved (Vidotti *et al.* 2004, Yan *et al.* 2004). More recently, analogous to the research developed by Eastman, layered clays like montmorillonite, talc, and mica were ion-exchanged with compatibilizers or surfactants and incorporated into PET by in-situ polymerization to improve gas barrier (Sekelik *et al.* 1999, Ke and Yongping 2005, Ke *et al.* 1999, Chang *et al.* 2004, Tsai *et al.* 2005). Most recently, layered double hydroxides (LDHs) were ion-exchanged with anionic surfactants dodecylsulfate, dodecylbenzene sulfate, and octylsulfate and incorporated into PET by melt-extrusion (Lee *et al.* 2006). Only the dodecylsulfate LDH was well exfoliated in the PET matrix, and consequently the thermal and mechanical properties were enhanced. This research is encouraging as only a select few PET nanocomposites are prepared with a layered oxide other than a layered silicate. However, gas barrier properties were not studied for this nanocomposite system.

Although PET is the polymer traditionally used for packaging materials, research into biodegradable packaging materials is being developed for environmental reasons. Montmorillonite was mixed into a biodegradable potato starch by melt blending (Avella *et al.* 2005), where complete intercalation of the starch into the interlayer galleries was achieved, as well as and increase in tensile strength and modulus. The nanocomposite films formed complied with European regulations for biodegradable materials and therefore could be used as alternative packaging materials. Gas barrier was not measured for these nanocomposites.

Epoxy-clay nanocomposites have also been well established for over a decade. Typically the clay layers are expanded with onium ions and then the epoxide, curing agent, or a mixture of both, are intercalated into the interlayer gallery regions of the clay (Messersmith and Giannelis 1994, Wang and Pinnavaia 1998). This has been a proven method to exfoliate the clay layers into the epoxy matrix which improves mechanical properties, thermal stability, and solvent resistance.

Similarly, the most successful polystyrene-clay nanocomposites were prepared by melt-intercalating the polymer above its melting point into the interlayer galleries that had been previously expanded by quaternary alkylammonium ions (Via *et al.* 1996). Another polystyrene (PS) nanocomposite was prepared by covalently modifying layered mesostructured aluminosilicates (LMAS) with hexadecyl groups and mixing the organo-alumniosilicate with polystyrene by microcompounding (Chastek *et al.* 2005). The PS-LMAS had increased elastic modulus and strength. Although the LMAS were well dispersed, they appeared as stacks according to transmission electron microscopy images.

Poly(styrene-butadiene), a synthetic rubber copolymer, was intercalated into dioctadecyldimethyl ammonium exchanged montmorillonite by mixing the copolymer and the organoclay at 120 °C (Laus *et al.* 1997, Laus *et al.* 1998). The nanocomposite formed showed an increased storage modulus. Natural rubber reinforced with organo-montmorillonite resulted in a 350% increase in strength without sacrificing the elasticity (Arroyo *et al.* 2003). Other research in rubber nanocomposites has indicated that silane modified kaolinite increases the compatibility between the hydrophilic clay and the rubber matrix, thus reinforcing the rubber (Dai and Huang 1999).

A polypropylene-bentonite nanocomposite is a yet another example of a clay that has been organically modified with a quaternary organic salt and that was added to a polymer matrix (Dai and Huang 1999). Bentonite, a layered aluminosilicate similar in structure to montmorillonite, was mixed with polypropylene using a batch mixer at 150-210 °C at a 1-5 wt. % loading. The main result obtained was that the nanocomposites containing organo-bentonite had a higher thermal stability than nanocomposites formed with natural clays. The authors explain this phenomenon by the formation of a nano structure that reduced diffusion of oxygen into the material.

While the above nanocomposite materials mostly utilized layered silicates to reinforce the polymer matrix, other layered oxides are being incorporated into polymer matrices for use as electrolyte materials and conducting nanocomposites, among others. An example of a PET-LDH nanocomposites was briefly presented earlier, but other LDH polymer nanocomposite systems are being studied. In contrast to silicates, LDHs have a positive charge on brucite-like Mg(OH)2 layers, which can be compensated for by anions or polymeric anions (Wilson *et al.* 1999). This results in an interesting layer chemistry of the materials and makes them attractive for applications such as ion-exchange, catalysis, and even as antacids (Constantino and Pinnavaia 1995, Ookubo *et al.* 1993, Playle *et al.* 1974). Early research in polymer-LDH research was based on intercalation of anionic polymers poly(styrenesulfonate) (PSS) and poly(vinylsulfonate) (PVS) into the galleries of a carbonate-containing LDH, confirmed by an increase in the interlayer spacing by X-ray diffraction (Wilson *et al.* 1999). Similarly, another LDH was modified by ion-exchange with sodium dodecylsulfate or polyoxyethylene sulfate to form biocompatible nanocomposites (Yang *et al.* 2005). Making use of the anion exchange capacity of LDHs, a poly(ethylene oxide) (PEO)-LDH was prepared for potential use as a polymer electrolyte (Liao and Ye 2004). An oligo(ethylene oxide) (OEO) modified LDH was made by a template method and then subsequently mixed with PEO. The LDH layers remained well exfoliated due to the compatibility between the OEO and the PEO. The PEO-LDH nanocomposite exhibited a substantial enhancement in conductivity compared to the pristine PEO.

Recently, nanosheets of layered metal oxides have attracted interest as additives for nanocomposite electrolytes because of their physicochemical properties and ability to be intercalated with various species (Pang *et al.* 2005). Specifically, polyaniline-vanadium oxide nanocomposites are being explored because of their mixed electronic charge-transport properties (Wu *et al.* 1996).

A polyaniline-V2O5 nanocomposite was formed by in-situ polymerization of aniline intercalated into the layered V2O5 under hydrothermal conditions (Pang *et al.* 2005). Polyaniline- V2O5 nanocomposite sheets formed with a thickness between 10-20 nm and lateral dimensions on the range of hundreds of nanometers to several microns. Poly(ethylene oxide) (PEO) was also intercalated into a lithium trivanadate, LiV3O8, to prepare a solid polymer electrolyte with potential applications in lithium batteries.53 PEO is widely doped with lithium salts but efforts are underway to improve the conductivity of the doped-PEO. LiV3O8 is a promising material for lithium batteries because the structure allows for reversible ion-exchange of lithium cations. When the PEO is mixed with the LiV3O8 under semi-hydrothermal conditions, the PEO partially exfoliates the LiV3O8 layers. The PEO- LiV3O8 nanocomposite showed a higher ionic conductivity than LiV3O8 and other lithium salt polymer electrolytes (Yang *et al.* 2005). This research

is a step towards the incorporation of other layered lithium containing metal oxides into polymers to form conducting nanocomposites. PEO was also introduced into the interlayer galleries of HNbWO6·1.5 H2O using melt-intercalation for another potential solid polymer electrolyte (Sairam and Viswanathan 2002). HNbWO6·1.5 H2O has a tetragonal structure with layers of NbWO6 slabs made up of Nb/W oxygen octahedra, separated by interlayer water molecules. It was found that as the intercalation time (i.e. heating of a HNbWO6·1.5 H2O -PEO pressed pellet to 75 ºC) was increased, the conductivity also increased.

Finally, and most recently, layered zirconium phosphates were synthesized and exfoliated into platelets with a high aspect ratio (>1000) for incorporation into various polymer matrices (Alberti *et al.* 2007, Sun *et al.* 2007, Zhang *et al.* 2007). The zirconium phosphates (ZrP) have an advantage over layered clays because of synthetic control over the dimensions and surface functionalities (Sun *et al.* 2007). A layered ZrP, Zr(HPO4)2·H2O was exfoliated using tetrabutylammonium hydroxide (TBA+OH-), and then the exfoliated platelets were isolated after centrifugation. These TBA+ exchanged platelets were then re-dispersed into acetone and mixed with an epoxy monomer. The acetone was evaporated and a curing agent was added to form an epoxy nanocomposite containing well exfoliated ZrP platelets with high aspect ratio (Sun *et al.* 2007). Similarly, ZrP was exfoliated using alkylamines and intercalated with an acrylamide monomer, which was subsequently polymerized to form a polyacylamide-ZrP nanocomposite (Zhang *et al.* 2007). This nanocomposite had improved thermal stability, most likely from the retardant effect of the exfoliated ZrP layers. A Nafion membrane was also prepared with the addition of the same ZrP to enhance the stability of proton conductivity at higher temperatures, by increasing the stiffness of the composite membrane (Alberti *et al.* 2007).

These examples of successful nanocomposites reiterate the fact that research in this area is promising and a plethora of nanocomposite materials are being explored for a wide variety of applications. However, there are still obstacles present, such as incomplete exfoliation of the oxide, incompatibility of the oxide and the polymer, and the sacrifice of some properties for the enhancement of others. Ongoing research aims at finding ways to overcome these obstacles and to produce quality nanocomposites with improved gas barrier property and ideally, enhancements in mechanical properties as well. As an in-depth example of one type of polymer nanocomposite, a summary of the structure, properties, and preparation of PET based polymer nanocomposites is given below.

1.2. POLYETHYLENE TEREPHTHALATE

Polyethylene terephthalate (PET) is a polyester that is used in a variety of industrial applications, especially in the food and beverage industry as packaging material. Therefore it is imperative that the PET packaging retains a barrier to gases such as carbon dioxide and oxygen, as well as water vapor. PET has many desirable properties for a packaging material including clarity, color, processability, chemical resistance, recyclability and, most importantly for food and beverage containers, tastelessness (Matayabas and Turner 2000). However, PET alone has minimal gas barrier and, therefore, using it as packaging for foods and beverages that are sensitive to oxygen or loss of carbon dioxide is problematic. Thus, there has been a recent thrust in nanocomposite research to improve the gas barrier of PET, so that the shelf-life of

products like beer, wine, and tomato-based products can be extended. Matayabas *et al.* 2000, Sekelik *et al.* 1999, Kim and Kim 2007, Matayabas and Turner 2000).

PET has been produced commercially for over 50 years, and is manufactured from ethylene glycol (EG) and terephthalic acid (TPA) or dimethylterephthalate (DMT) (Kim and Kim 2007). The polymerization of PET requires two main steps, transesterification or direct esterification, followed by polycondensation. Both esterification processes produce BHET, an oligomeric precursor to PET. In the final step excess EG is removed upon heating BHET to about 280°C during polycondensation to form PET. This reaction scheme is shown in Figure 1.3.

Once PET is formed, there are two main methods of dispersing the additives to prepare nanocomposites: melt-blending or in-situ polymerization (Kim and Kim 2007, LeBaron *et al.* 1999, Tsai 2000, Ray and Okamoto 2003). Melt-blending involves mixing the polymer and the additive above the melting point of the polymer under high shear force. Melt-blending is typically used industrially to produce large scale quantities of PET, so it is advantageous to produce nanocomposites by the same method. However, the main difficulty lies in successfully exfoliating the layered additives by shear force alone. Few have reported the successful formation of PET nanocomposites by this method (Davis *et al.* 2001, Lyatskaya and Balazs 1998). For in-situ polymerizations, a PET monomer is intercalated into the layered structure, and subsequently polymerized. The most important advantage of this method is the fact that exfoliation of the layers is promoted and maintained by the presence of the intercalated polymer. As discussed earlier, exfoliation is a key to producing quality nanocomposites. The main disadvantage is that large-scale production of nanocomposites by this method is a difficult and time-consuming task.

1.3. LAYERED OXIDES

As previously mentioned, layered oxides are good candidates for nanocomposite additives because their layered structure allows for exfoliation and subsequent incorporation into polymer matrices. Simply stated, layered oxides are any oxygen-containing layered material such as, cuprates, titanates, phosphonates, niobates, or silicates. However, layered silicates are the most utilized layered material in the vast majority of ongoing research in layered-oxide nanocomposites. Layered silicates, or phyllosilicates, represent a large class of clay minerals that are distinguished by layers of silicate sheets coordinated to other metal-oxygen sheets. Groups in this class include micas, kaolins, vermiculites, chlorites, talc, pyrophyllite, and smectites. Smectites are the largest and one of the most widely studied groups because they are common in temperate soils, and have a high cation exchange capacity and a large aspect ratio (Carrado *et al.* 2001, Carrado 2004, Kloprogge *et al.* 1999). Two of the most researched smectites of this structure type are montmorillonite and hectorite. Montmorillonite is a readily available clay, while hectorite is an easily synthesized clay via mild conditions. Montmorillonite and hectorite are the preferred layered materials for polymer nanocomposite systems (Alexandre and Dubois 2000, Carrado 2003, Chang *et al.* 2003, Gopakumar *et al.* 2002, Loo and Gleason 2004, Maiti *et al.* 2002, Matayabas and Turner 2000, Nielsen 1967, Pinnavaia and Beall 2000, Strawhecker and Manias 2000).

Another layered silicate, magadiite, is a member of a class of materials known as layered hydrous sodium (or alkali) polysilicates that also includes kanemite, makatite, kenyaite and octosilicate. Their structure is made up of negatively charged tetrahedral

silicate layers balanced by sodium cations. Magadiite has an even higher cation exchange capacity and aspect ratio compared to the smectites, and is easily synthesized under semi-hydrothermal conditions (Feng and Balkus 2003, Kooli *et al.* 2006, Kwon *et al.* 1995, Kwon and Park 2004, Peng *et al.* 2005, Schwieger and Lagaly 2004, Wang *et al.* 2006, Zhang *et al.* 2003). Research has shown that the incorporation of exfoliated magadiite layers into epoxy nanocomposites has increased the tensile strength of the epoxy matrix, while still maintaining transparent optical properties (Wang *et al.* 1996, Wang and Pinnavaia 1998). To date, research of magadiite nanocomposites for improved gas barrier properties is limited.

Theoretically, based on the gas barrier models presented in the following section, these layered silicates alone should improve the gas barrier of nanocomposites. However, unfavorable interactions between the hydrophilic silicates and the hydrophobic polymer may have a negative impact on other physical and mechanical properties. Therefore, the silicates are typically modified by covalently attaching organic functionalities to the surface hydroxyl groups, or by ion-exchanging with alkylammonium cations to expand the layers, and subsequently modify the interlayer surfaces (Peng *et al.* 2005, Zhang *et al.* 2003, Fujita *et al.* 2003, Isoda and Kuroda 2000, Ogawa *et al.* 1998, Okutomo *et al.* 1999, Wang *et al.* 2004).

1.4. NANOCOMPOSITE THEORY

There are three scenarios that can occur when a layered oxide is mixed with a polymer (Figure 1.1). First, the oxide can remain ordered and unexfoliated, forming a phase-separated composite. These conventional composites might have improved rigidity, but might sacrifice other properties such as elongation and toughness (LeBaron *et al.* 1999). Insertion of a polymer matrix into the layered silicate structure results in an intercalated nanocomposite, where the silicate layers remain ordered, but interfacial surface area between the silicate and polymer is greatly increased. This improves chemical, structural, and thermal stabilities compared to the polymer alone (Komori and Kuroda 2000). Finally, the best-case scenario would be complete exfoliation of the silicate layers well dispersed into the polymer. In this case, the clay-polymer interactions are maximized, and thus the chemical, physical, and mechanical properties are greatly enhanced. However, complete exfoliation is often a difficult task. Variables such as choice of matrix, process of incorporating the layered additive, choice of additive, treatment of additive (organic modification), and use of dispersing aids must be carefully considered (Matayabas and Turner 2000). Since exfoliation has been determined to have a profound effect on the performance of nanocomposites, a high aspect ratio of the separated layers would further improve the performance. Therefore, nanocomposites containing well-exfoliated silicate layers with the highest aspect ratio, to maximize the clay-polymer interactions, achieve the best results.

Aspect ratio (α) is defined as the ratio of the lateral dimensions to the thickness of an exfoliated silicate platelet. Since the platelets are often irregular, the aspect ratio becomes

$$\alpha = \frac{\sqrt{A}}{Z} \tag{1}$$

where A is the area of the platelet face, and Z is the thickness of the platelet (Auddy 2007, Kloprogge *et al.* 1999, Liu 2005, Ploehn and Liu 2006). It has been found that aspect ratio is crucial for improving certain properties, such as gas barrier (Alexandre and Dubois 2000, Jang and Lee 2004, Tsai 2000, Matayabas and Turner 2000). Nielsen developed the "tortuous path" theory to explain how aspect ratio effects the permeability of gases through a polymer (Alberti *et al.*, 2007). An approximation of the permeability ratio can be represented as

$$\frac{P_n}{P_m} = \frac{\phi_p}{\tau} \tag{2}$$

where Pn is the permeability of the nanocomposite and Pm is the permeability of the unfilled polymer matrix, ϕp is the volume fraction of the polymer, and τ is the tortuosity factor. The tortuosity factor is defined as the distance a gas molecule must travel through a polymer film divided by the thickness of the film. This factor is dependent on the aspect ratio in the following relationship:

$$\tau = 1 + \alpha\phi_f \tag{3}$$

where ϕf is the volume fraction of filler additives and therefore equation 2 becomes

$$\frac{P_n}{P_m} = \frac{\phi_p}{1 + \alpha\phi_f} \tag{4}$$

for ideal nanocomposite systems. This model is represented schematically in Figure 1.2, where exfoliated platelets provide a more "tortuous path" for the gas to diffuse through the polymer. A barrier improvement factor (BIF) can be estimated from the permeabilities, where

$$BIF = \frac{P_m}{P_n} \tag{5}$$

and the BIF is used to quantify the barrier improvement of nanocomposites (Liu 2005, Matayabas and Turner 2000, Nielsen 1967). More advanced models were also developed to account for overlapping in "semi-dilute" nanocomposites systems (Matayabas and Turner 2000, Nielsen 1967). Based on calculated aspect ratios of synthesized silicates, the barrier improvement of a nanocomposite can be predicted from this theoretical model and compared to experimental BIF values determined by various methods. More advanced models were also developed to account for overlapping in "semi-dilute" nanocomposites systems (Cussler *et al.*, 1998).

1.5. SUMMARY

Polymer nanocomposites are an exciting and active research area that promises new materials with enhanced properties. These polymer nanocomposites consist of nano-sized additives that are uniformly dispersed in a polymer host matrix, to generate substantial enhancements in physical properties relative to those of the pristine polymers. Research in nanocomposites has shifted towards layered oxides as the preferred additive, as their layered structure allows for exfoliation, or separation of layers, which increases the aspect ratio, and subsequently property enhancements.

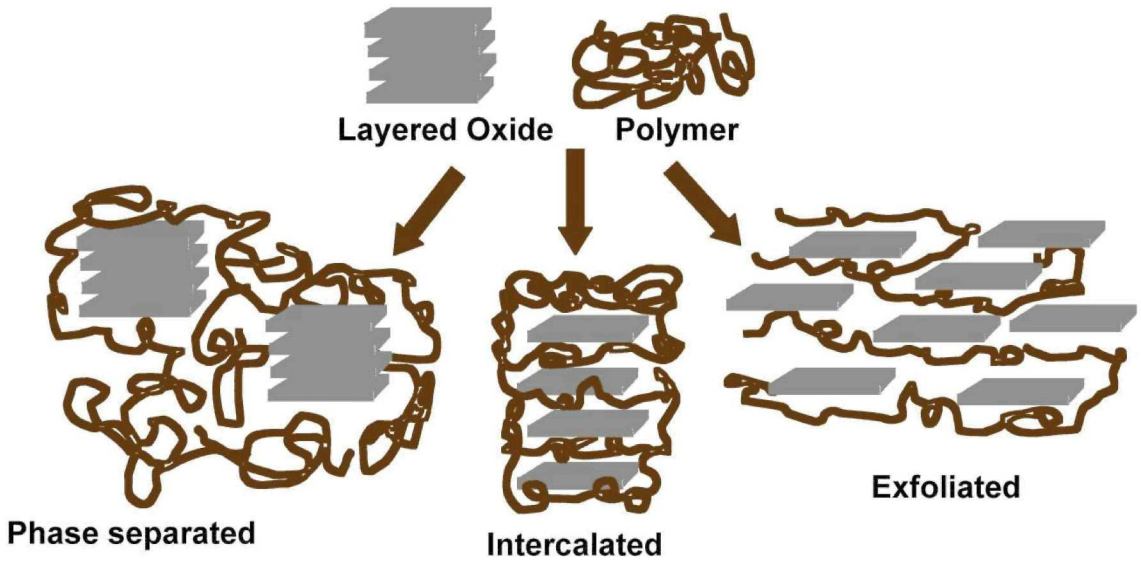

Figure 1.1. Schematic illustrations of three possible scenarios for dispersion of layered oxides in a polymer matrix.

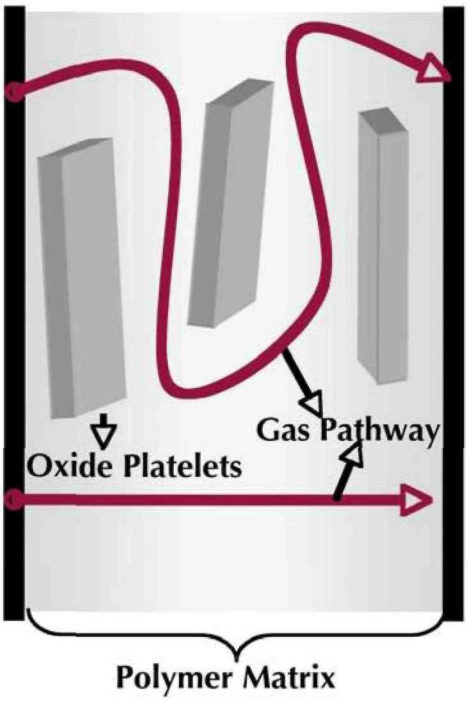

Figure 1.2. Illustration of the "tortuous path" model. Oxide platelets increase the path length of the gas, causing a reduction in permeablitity.

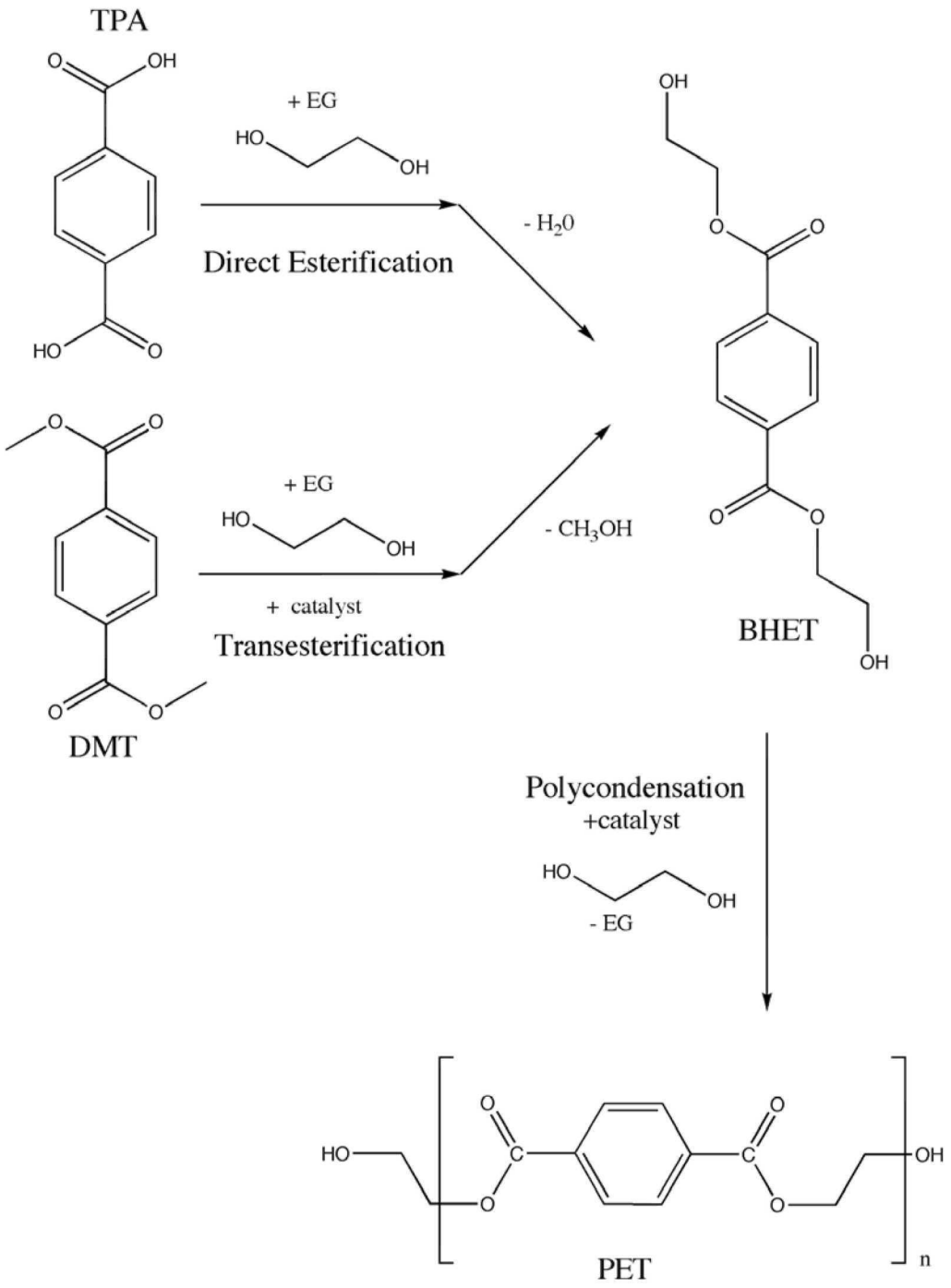

Figure 1.3. Reaction scheme for the PET polymerization process.

LITERATURE CITED

Alberti, G, Casciola M, Capitani D, Donnadio A, Narducci R, Pica M, Sganappa M. 2007. Electrochimica Acta. 52, 8125-8132.

Alexandre M, Dubois P. 2000. Materials Science and Engineering. 28, 1-63.

Alexandre M, Dubois P, Sun T, Garces J M, Jerome R. 2002 Polymer. 43, 2123-2132.

Arroyo M, Lopez-Manchado MA, Herrero B. 2003. Polymer. 44, 2447-2453.

Auddy, K. Synthesis and Characterization of PET Nanocomposites. 2007. University of South Carolina, Columbia, SC.

Avella M, De Vlieger JJ, Errico ME, Fischer S, Vacca P, Volpe MG. 2005. Food Chemistry. 93, 467-474.

Bharadwaj RK, Mehrabi AR, Hamilton CB, Trujillo C, Murga M, Fan R, Chavira A, Thompson AK. 2002. Polymer. 43, 3699-3705.

Carrado KA, Xu L, Csencsits R, Muntean JV. 2001. Chemistry of Materials. 13, 3766-3773.

Carrado KA. 2003. Polymer-Clay Nanocomposites. In Advanced Polymeric Materials, Shonaike, G. O, Advani, S. G., Eds. CRC Press: Boca Raton. pp 349-396.

Carrado KA. 2004. In Handbook of Layered Material, Auerbach, S. M, Carrado, K. A, Prabir, K. D., Eds. Marcel Dekker, Inc.: New York. pp 1-38.

Chang JH, Yeong UA. 2002. Journal of Polymer Science: Part B: Polymer Physic. 40, 670.

Chang JH, An YU, Cho D, Giannelis EP. 2003. Polymer. 44, 3715-3720.

Chang JH, Kim SJ, Joo YL, Im S. 2004. Polymer. 43, 919.

Chastek TT, Stein A, Macosko C. 2005. Polymer. 46, 4431-4439.

Constantino VRL, Pinnavaia TJ. 1995 Inorganic Chemistry. 34, 883-892.

Cussler EL, Hughes SE, Ward WJ, Rutherford A. 1998. Journal of Membrane Science. 38, (2), 161-174.

Dai JC, Huang JT. 1999. Applied Clay Science. 15, 51.

Davis CH, Mathias LJ, Gilman JW, Schiraldi D, Davis A, Shields JR, Truelore P, Sutto TE, Delong HC. 2001. Journal of Polymer Science: Part B: Polymer Physics. 40, (23), 2661-2666.

Feng F, Balkus J. 2003. Journal of Porous Materials. 10, 5-15.

Fornes TD, Yoon PJ, Hunter DL, Kekkula H, Paul DR. 2002. Polymer. 43, 5915.

Fujita I, Kuroda K, Ogawa M. 2003. Chemistry of Materials. 15, 3134-3141.

Garces JM, Moll DJ, Bicerano J, Fibiger R, McLeod DG. 2000. Advanced Materials. 12, (23), 1835-1839.

Gilman JW, Jackson CL, Morgan AB, Harris JR, Manias E, Giannelis EP, Wuthenow M, Hilton D, Phillips SH. 2000. Chemistry of Materials. 12, 1866-1873.

Gopakumar, TG, Lee JA, Kontopoulou M, Parent JS. 2002. Polymer. 43, 5483-5491.

Grunlan JC, Grigorian A, Hamilton CB, Mehrabi AR. 2004. Journal of Applied Polymer Science. 93, 1102.

Hoffmann B, Dietrich C, Thomann R, Friedrich C, Mulhaupt R. 2000. Macromolecular Rapid Communications. 21, 57-61.

Imai Y, Inukai Y, Tateyama H. 2003. Polymer Journal. 35, (3), 230.

Isoda K, Kuroda K. 2000. Chemistry of Materials. 12, 1702-1707.

Jang J, Lee DK. 2004. Polymer. 45, 1599-1607.

Jordan J, Jacob KI, Tannenbaum R, Sharaf MA, Jasiuk I. 2005. Materials Science and Engineering. 393, 1-11.

Ke Y, Long C, Qi Z. 1999. Journal of Applied Polymer Science. 71, 1139-1146.

Ke Y, Yongping B. 2005. Materials Letters. 59, 3348-3351.

Kim SH, Kim SC. 2007. Journal of Applied Polymer Science. 103, 1262-1271.

Kloprogge JT, Komarneni S, Amonette JE. 1999. Clays and Clay Minerals. 47, (5), 529-554.

Kojima Y, Usuki A, Kawasumi M, Okada A, Fukushima Y, Kurauchi T, Kamigaito O. 1993. Journal of Materials Research. 8, (5), 1185-1189.

Komori Y, Kuroda K. 2000. In Polymer-Clay Nanocomposites. Pinnavaia, TJ, Beall, GW., Eds. John Wiley and Sons, Inc. New York. pp 3-18.

Kooli F, Mianhui L, Alshahateet SF, Chen F, Yinghuai Z. 2006. Journal of Physics and Chemistry of Solids. 67, 926-931.

Kwon OY, Jeong SY, Suh JK, Lee JM. 1995. Bulletin of the Korean Chemical Society. 16, (8), 737-741.

Kwon OY, Park KW. 2004. Bulletin of the Korean Chemical Society. 25, (1), 25-26.

Laus M, Francescangeli O, Sandrolini F, 1997. Journal of Materials Research. 12, 3134-3139.

Laus M, Camerani M, Lelli M, Sparnacci K, Sandrolini F. 1998. Journal of Materials Science. 33, 2883-2888.

LeBaron PC, Wang Z, Pinnavaia TJ. 1999. Applied Clay Science. 15, 11-29.

Lee WD, Im SS, Lim HM, Kim KJ. 2006. Polymer. 47, 1364-1371.

Liao CS, Ye WB. 2004. Electrochimica Acta. 49, 4993-4998.

Liu C. 2005. Characterization of Platelet Materials and PET-Montmorillonite Nanocomposites. University of South Carolina, Columbia, SC.

Loo LS, Gleason KK. 2004. Polyme. 45, 5933-5939.

Lyatskaya Y, Balazs AC. 1998 Macromolecules. 31, 6676.

Maiti P, Yamada K, Okamoto M, Ueda K, Okamoto K. 2002. Chemistry of Materials., 14, 4654.

Matayabas, JC, Turner SR, Sublett BJ, Connell GW, Gilmer JW, Barbee RB, High IV. 2000. Polyester Compositions Containing Platelet Particles. 6,084,019, 7/4/2000.

Matayabas Jr. JC, Turner SR. 2000. In Polymer-Clay Nanocomposites, Pinnavaia TJ, Beall GW, Eds. John Wiley & Sons, Ltd.: New York. pp 207-225.

Messersmith PB, Giannelis EP. 1994. Chemistry of Materials. 6, 1719-1725.

Nielsen LE. 1967. Journal of Macromolecular Science (Chemistry). A1, (5), 929-942.

Ogawa M, Miyoshi M, Kuroda K. 1998. Chemistry of Materials. 10, 3787-3789.

Okutomo S, Kuroda K, Ogawa M. 1999. Applied Clay Science. 15, 253-264.

Ookubo A, Ooi K, Hayashi H. 1993. Langmuir. 9, 1418-1422.

Pang S, Li G, Zhang Z. 2005. Macromolecular Rapid Communications. 26, 1262-1265.

Peng S, Gao Q, Du Z, Shi J. 2005. Applied Clay Science. 31, (3-4), 229-237.

Pinnavaia , TJ, Beall GW. 2000. Polymer-Clay Nanocomposites. John Wiley & Sons, Ltd.: Chichester. p 349.

Playle AC, Gunning SR, Llewellyn AF. 1974. Pharm. Acta. Helv. 49, 298-302.

Ploehn HJ, Liu C. 2006. Ind. Eng. Chem. Research. 45, 7025-7034.

Ray SS, Okamoto M. 2003. Prog. Polymer. Science. 28, 1539-1641.

Sairam TN, Viswanathan B. 2002. Journal of Physics and Chemistry of Solids. 63, 317-322.

Schmidt D, Shah D, Giannelis EP. 2002. Current Opinion in Solid State and Materials Science 6, 205.

Schwieger W, Lagaly G. 2004. Alkali Silicates and Crystalline SIlicic Acids. In Handbook of Layered Materials, Auerbach, SM, Carrado, KA, Dutta, PK., Eds. Marcel Dekker, Inc. New York.

Sekelik DJ, Stepanov EV, Nazarenko S, Schiraldi D, Hiltne, A, Baer E. 1999. Journal of Polymer Science: Part B: Polymer Physics. 37, 847.

Strawhecker KE, Manias E. 2000. Chemistry of Materials. 12, 2943-2949.

Sun L, Boo WJ, Sun D, Clearfield A, Sue HJ. 2007. Chemistry of Materials. 19, 1749-1754.

Tsai TY. 2000. In Polymer-Clay Nanocomposites. Pinnavaia, TJ, Beall, GW., Eds. John Wiley and Sons, Ltd.: New York. pp 173-189.

Tsai TY, Li CH, Chang CH, Cheng WH, Hwang CL, Wu RJ. 2005. Advanced Materials. 17, 1769-1773.

Usuki A, Kojima Y, Kawasumi M, Okada A, Fukushima Y, Kurauchi T, Kamigaito O. 1993. Journal of Materials Research. 8, (5), 1179-1184.

Utracki LA, Sepehr M, Boccaleri E. 2007. Polymers for Advanced Technologies. 18, 1-37.

Vaia R, Jandt KD, Kramer EJ, Giannelis EP. 1996. Chemistry of Materials. 8, 2628.

Vidotti SE, Chinellato AC, Boesel LF, Pessan LA. 2004. Journal of Metastable and Nanocrystalline Materials. 22, 57-64.

Wang D, Jiang DD, Pabst J, Han Z, Wang J, Wilkie CA. 2004. Polymer Engineering and Science. 44, (6), 1122-1131.

Wang YR, Wang SF, Chang LC. 2006. Applied Clay Science. 33, 73-77.

Wang Z, Lan T, Pinnavaia TJ. 1996. Chemistry of Materials. 8, 2200-2204.

Wang Z, Pinnavaia TJ. 1998. Chemistry of Materials. 10, 1820-1826.

Wilson Jr. OC, Olorunyolemi T, Jaworski A, Borum L, Young D, Siriwat A, Dickens E, Oriakhi C, Lerner M. 1999. Applied Clay Science. 15, 265-279.

Wu CG, DeGroot DC, Marcy HO, Schindler JL, Kannewurf CR, Liu YJ, Hirpo W, Kanatzidis MG. 1996. Chemistry of Materials. 8, 1992.

Yan M, Pan X, Wan C. 2004. Polymers and Polymer Composites. 12, 619-625.

Yang G, Hou W, Sun Z, Yan, Q. 2005. Journal of Materials Chemistry. 15, 1369-1374.

Yang QZ, Ling JY, Zhang CK. 2005. Journal of Materials Science. 40, 3287-3291.

Zhang R, Hu Y, Li B, Chen Z, Fan W. 2007. Journal of Materials Science. 42, 5641-5646.

Zhang Z, Saengkerdsub S, Dai S. 2003. Chemistry of Materials. 15, 2921-2925.