UNIVERSITI PUTRA MALAYSIA

PREPARATION AND CHARACTERISATION OF LAYERED METAL HYDROXIDES INTERCALATED WITH CIPROFLOXACIN AND ETHACRYNIC ACID FOR SLOW DRUG RELEASE

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By

AHMAD FAIZ BIN ABDUL LATIP

Thesis submitted to the School of Graduate Studies, Universiti Putra Malaysia, in Fulfilment of the Requirement for the Degree of Doctor of Philosophy

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Chair: Professor Mohd. Zobir bin Hussein, PhD
Faculty: Institut Teknologi Maju

In this study, two model drugs, ciprofloxacin (CFX) and ethacrynic acid (ECA) are intercalated in layered zinc hydroxides (LZH) and layered double hydroxides (LDH) host materials via either anion exchange or co-precipitation methods. Four intercalation compounds are obtained, designated as Z–CFX, AEZ–ECA, CPZ–ECA and MAL–ECA according to their materials and method of synthesis. Powder X-ray diffraction suggests that CFX and ECA were successfully intercalated in the interlayer region of their respective hosts, as indicated by the interlayer spacing expansion. The co-precipitation method gives a larger interlayer spacing value for CPZ–ECA compared to that of the anion exchange value in AEZ–ECA. This suggests the advantage of employing the former method over the latter in the intercalation of large organic molecule in the LMH hosts. Fourier transform infrared spectroscopy further confirms the intercalation of the CFX and ECA in the host interlayers when the absorption bands of carboxylate groups of the drugs emerge in the FTIR spectra, indicating both drugs were intercalated in an anionic form. The wavenumber differences of the carboxylate absorption bands reveal that the intercalated drugs were bonded to the metal cations of the host lattices via a unidentate coordination mode. Thermal analysis exhibits that the thermal properties of all the intercalated drugs were enhanced compared to that of the non-intercalated ones, possibly due to chemical interactions between the intercalated anionic drugs and the host lattices. A faster release behavior was demonstrated in phosphate-buffered saline (PBS) solution at pH 6.0 compared to that of pH 7.4. The

release mechanisms are varied amongst the intercalation compounds, indicating different processes were involved during the release of the intercalated anions. The cytotoxicity was evaluated against VERO and A549 cell lines for 72 hours. The ECA–intercalated LMH compounds (AEZ–ECA, CPZ–ECA and MAL–ECA) were not toxic to both cell lines, whereas Z–CFX showed enhanced toxicity compared to that of the free CFX molecule. This study demonstrates the potentials of LMH materials as drug carriers based on the slow release behavior and the reduced toxicity profile of the intercalation compounds toward the VERO and A549 cell lines, especially concerning the ECA–intercalated LMH compounds.

Abstrak tesis yang dikemukakan kepada Senat Universiti Putra Malaysia sebagai memenuhi keperluan untuk ijazah Doktor Falsafah

PENYEDIAAN DAN PENCIRIAN BAHAN LOGAM HIDROKSIDA BERLAPIS TERSISIP DENGAN CIPROFLOXACIN DAN ASID ETHACRYNIC BAGI TUJUAN PELEPASAN UBAT SECARA PERLAHAN-LAHAN

Oleh

AHMAD FAIZ BIN ABDUL LATIP

Mei 2014

Pengerusi: Professor Mohd. Zobir bin Hussein, PhD
Fakulti: Institut Teknologi Maju

Dalam kajian ini, dua molekul ubat ciprofloxacin (CFX) and ethacrynic acid (ECA) telah disisipkan ke dalam dua kelas perumah iaitu zink hidroksida berlapis (LZH) dan hidroksida berlapis ganda (LDH) samada melalui kaedah tindakbalas penukargantian anion atau tindakbalas pemendakan serentak. Sebanyak empat sebatian tersisip telah diperoleh, iaitu Z–CFX, AEZ–ECA, CPZ–ECA and MAL–ECA, masing-masing dinamakan mengikut bahan yang terkandung dan kaedah sintesis yang digunakan. Serakan sinar hablur X-ray (XRD) mencadangkan bahawa CFX and ECA telah berjaya disisipkan di ruangan antara lapisan-lapisan perumah masing-masing, seperti yang dibuktikan menerusi pertambahan jarak di antara lapisan-lapisan perumah tersebut. Kaedah pemendakan serentak menyebabkan kenaikan jarak yang lebih tinggi pada CPZ–ECA berbanding jarak yang dicatat oleh AEZ–ECA yang dicapai secara penukargantian anion. Dapatan ini mencadangkan kelebihan kaedah pemendakan serentak berbanding penukargantian anion bagi penyisipan molekul organik yang bersaiz besar ke dalam perumah-perumah LMH. Spektroskopi Fourier terubah inframerah (FTIR) mengukuhkan dapatan daripada XRD bahawa penyisipan CFX dan ECA telah berjaya apabila jalur-jalur serapan kumpulan karboksilat pada molekul ubat tersebut muncul dalam spektrum-spektrum FTIR. Kemunculan ini mencadangkan bahawa kedua-dua ubat telah tersisip dalam bentuk anion. Perbezaan pada angkagelombang (wavenumber) jalur-jalur serapan karboksilat

mendedahkan bahawa ubat-ubat yang tersisip adalah terikat dengan logam kation pada lattis (lattice) perumah secara koordinasi unidentat. Analisis termal menunjukkan bahawa sifat termal bagi semua ubat yang tersisip telah dipertingkat berbanding sifat termal yang dipunyai oleh ubat yang tidak tersisip. Hal ini mungkin disebabkan oleh interaksi kimia di antara ubat tersisip yang berbentuk anion dengan kekisi perumah. Tingkahlaku pelepasan dalam larutan PBS pada pH 6.0 didapati lebih cepat daripada pelepasan pada pH 7.4. Mekanisme pelepasan yang tidak seragam di antara sebatian-sebatian tersisip dalam kedua-dua pH larutan mencadangkan kerencaman proses yang terlibat semasa pelepasan anion tersisip. Ujian sitotoksisiti dijalankan terhadap baris-baris sel VERO dan A549 selama 72 jam. Sebatian LMH tersisip ECA didapati tidak toksik terhadap kedua-dua baris sel manakala ketoksikan Z–CFX didapati meningkat berbanding ketoksikan molekul bebas CFX. Kajian ini menunjukkan bahan LMH berpotensi sebagai pengangkut ubat berasaskan kepada tingkahlaku pelepasan perlahan dan kadar ketoksikan yang turun terhadap baris-baris sel VERO dan A549, terutamanya yang membabitkan ketiga-tiga sebatian LMH yang tersisip dengan ECA.

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CHAPTER 1

INTRODUCTION

1.1 Nanotechnology in Drug Delivery Systems

There have been concerted efforts since the last few decades aiming to understand phenomena at atomic and molecular levels as the burgeoning interests swept across various segments of scientific community. Scientists were largely driven by the notion that there is "plenty of room at the bottom" (*1*). This phrase which had transpired during a lecture by Richard Feynman in 1959 laid out the vast possibilities that one could do or make for being able to manipulate or control individual atoms and molecules (*2*). Chronologically, the term nanotechnology first gained public attention when it was coined in 1974 (*3*), followed by publication of arguably one of the most popular book on nanotechnology in 1986 (*4*). Furthermore, nanotechnology was very much embraced by mass media, which had helped popularized the notion throughout the globe via a myriad of channels, which include motion pictures, documentaries, news broadcast, interviews, electronic games and many more.

Nanotechnology can be defined as research and development (R&D) activities aimed at gaining understanding into materials and phenomena occurring at atomic and molecular levels, generally in the range of 1–100 nm or the nanometer scale, in order to design or devise materials or systems that have novel properties and functions (*5*). One research field where nanotechnology is expected to make significant impact is drug delivery systems (DDS). This field which mainly deals with the R&D on drug carriers is a vibrant discipline and is making a rapid progress by virtue of nanotechnology (*6–8*).

A number of critical issues in DDS, which are largely centered on physico-chemical properties of host–drug systems (*9*), as well as cytotoxicity of the drug carrier (*10*), are being addressed by manipulating the atomic and molecular interactions through the state-of-the-art instrumentations and analytical tools. The synergy of DDS and nanotechnology is attracting a large pool of scientists from a wide range of disciplines; chemistry, physics, material science, pharmacology, toxicology and a few more others to converge on ground-breaking researches toward providing solutions in critical areas such as cancer treatment, brain diseases and gene therapy (*11–13*). Emerging research fields such as biomaterials and nanotoxicology are inter-related and complementary to the DDS, which highlights the multidisciplinary nature of the field (*14–15*). On the other hand, the practice "from bench to bedside" is being implemented for translating highly potential research findings into clinical products (formulated drugs, medicinal devices, regenerative tissues) so they may benefit the whole society (*16*).

DDS is defined by Jain as "a formulation or a device that enables the introduction of a therapeutic substance in the body and improves its efficacy and safety by controlling the rate, time, and place of release of drugs in the body" (*17*). Amongst commonly employed therapeutic substances for DDS include protein, drugs, vaccine or DNA molecules (*18–21*). These organic components are mixed or combined with a wide array of host materials to give rise to novel DDS-based carriers suited for various therapeutic purposes (*22*). Additionally, the new generation of DDS-based carriers holds several advantages over the conventional drug administration, which include enhanced efficacy for suboptimal drugs and minimized side effects following the drug administration into the human body (*23–24*).

The history of modern DDS has its root in mid 1960s with the discovery of silicone rubber as a prolonged release drug carrier. This groundbreaking discovery had since then sparked great interests from the academics and the industry alike. Products of DDS were commercialized in early 1970s. Since its conception, the DDS field has undergone three major defining periods which underscore the dynamic nature of the field; (1) the "MACRO era", (2) the "MICRO era" and (3) the "NANO era". It has been four decades now for DDS with much more to

gain as the field being currently steered to the "BIO" era, capitalizing on the increased knowledge in molecular biology, as well as the abilities to design and control new generations of targeted nanosized drug carriers (*25*).

Back in the MACRO era of DDS, drug carriers were mainly constituted of bulk devices and macroscopic polymer matrices such as the ophthalmic device, Ocusert™ and the PEVA hydrophobic polymer used to release protein drugs (*25*). Through nanotechnology, the size of the carriers has been reduced down to the nanometer scale, giving rise to a new generation of nanosized drug carriers, or known as nanocarriers (*26*). Additionally, the new generations of nanocarriers can be deliberately designed toward achieving cell-specific targeted drug delivery systems (*27–28*). Equally important are the abilities to minimize the inherent toxicity of either the drug or the host carrier (*29*); these properties are realized by virtue of the nanotechnology applications. Numerous examples of drug nanocarriers range from polymeric nanoparticles, dendrimers, lipids and inorganic nanomaterials such as silica and gold nanoparticles (*30–34*), including an emerging class of layered inorganic solids such as clays and clay minerals, montmorrilonite and layered metal hydroxides (*35–36*).

1.2 Problem Statements

Layered materials are intriguing structures that are generally built from stacks of nanolayers (*37*). These materials are increasingly studied due to their abilities to incorporate a large number of molecules in their structures, prompting wide spread applications such as biopolymer composite (*36*), catalysis (*38*) and biomolecule reservoir (*39*).

A family of layered materials, commonly known as layered metal hydroxides (LMH) material, is established for its negatively charged layers that can intercalate various molecules in its interlayer space (*40–41*). Many studies on LMH materials are currently channeled toward synthesizing drug carriers based on the LMH compounds (*39, 42–43*). This is partly due to the relatively ease of synthesis and versatility of the material (*40*). A wide variety of drug molecules has been intercalated in

the LMH interlayers, ranging from non steroidal anti inflammatory drugs (NSAIDS) (*45–46*), anticancer agents (*47–48*), antihypercholestrolemia drug (*49*), antibiotics (*50–51*) and antihypertensive drug (*52*).

Ethacrynic acid (ECA) is a major diuretic drug that is used to treat edema, a condition where intake of sodium and water is not balanced by their excretion by the kidney (*53*). Basically, the drug inhibits sodium transport in the ascending thick segment of the loop of Henly (*54*). The pharmacological action of ECA is exerted by the phenoxyacetic acid group, which contributes to the diuretic and uricosuric activities of the drug (*55*). The diuretic agent is also a potential glaucoma drug in which it can reduce elevated intraocular pressure of the eye (*56*). Interestingly, ECA demonstrates potential therapeutic activities in cancer treatment, where the drug causes death to human colon cancer cell line DLD-1 (*57*), and it enhances toxicity of antineoplastic agents such as chlorambucil and melphalan against drug-resistant cell lines (*58*). The above features indicate the pleiotropic effects of ECA, the unique characteristics that may exert other pharmacological actions not limited only to the kidney (*59*).

ECA, however, suffers from first pass elimination (*55*), thus reducing its bioavailability where only a small fraction of the drug dosage reaches the systemic circulation. This effect is undesirable since the pharmacological actions of the drug are greatly reduced. It may also cause acute hearing loss, possibly due to the formation of cysteine conjugate that affects the cochlea (*55*). Long term administration of ECA may cause potassium depletion in cardiac patient or hepatic coma in the cirrhotic with ascites (*54*). Hyperuricemia and diminished uric acid excretion are also observed in some patients following prolonged administration of the diuretic agent (*60*). Co-administration of ECA with heparin has slightly raised the issue of toxicity since the former drug can cause the gastrointestinal bleeding (*61*).

The strategies of DDS provide indispensable opportunities for further enhancing the efficacy of ECA (*62, 63, 64*). Despite being one of the leading agents in diuretic therapy, however, report on the ECA application in DDS is considerably rare. To our knowledge, there are only two reports available, with the first report emerged in 1997 contributed by the group of Kalish where they studied the potential of

ECA as a counter-sensitizing agent for transdermal drug delivery (*65*). In this study, ECA was mixed into hydroxypropyl methylcellulose as a drug carrier and the group had found that the mixture inhibited sensitization to the skin when it was administered with various topically applied drugs. This paper, however, contains a very brief discussion on the synthesis method whereas the characterization aspect of the ECA-containing drug carrier was not included.

The second report was published in 2004 by Yuan and colleagues where they prepared poly(lactic-co-glycolide) (PLGA) copolymer film containing ECA for glaucoma treatment in ocular drug delivery (*66*). In this work, ECA was added into the PLGA film using a solvent casting technique whereas the release of ECA from the polymer film was studied in a phosphate-buffered saline (PBS) solution at pH 6.9. The cumulative release of ECA from the PLGA film was exhibited over a seven day period. However, the release kinetics of the ECA were not performed.

The present study seeks to employ the LMH materials as a drug host for ECA by exploiting its unique structure that can intercalate a wide array of drug molecules in its interlayers. The layered host offers a slight advantage over the use of the PLGA films in hosting the ECA molecules (*66*) due to its well-defined framework structures (*40*, *44*).The drug efficacy can also be enhanced upon its intercalation in the LMH interlayers (*67, 68, 69*). Moreover, one can conveniently determine the mechanisms of drug release of this LMH-based carrier owing to the established anion exchange property of the host material (*49, 52, 63, 70*).

In addition to ECA, ciprofloxacin (CFX), one of the most well known antibiotics in the family of fluoroquinolone, which is widely used to treat various bacterial infections, is also selected for intercalation into the LMH hosts. It is by far the best effective fluoroquinolone antibiotic toward the *Pseudomonas aeruginosa in vitro* (*71*). Basically, the antibacterial activity of CFX is exerted through the chelating effects of the drug structure with the target DNA/DNA gyrase complex of the bacteria cells (*72*).

However, antibacterial treatment with fluoroquinolones especially concerning CFX poses several toxicity issues which deserve attentions. CFX may cause hepatic failure due to accumulation in the liver (*73*). The bioavailability of CFX is reduced when it is co-administered with oral iron and multivitamin-zinc complex due to the chelating effects between the antibiotic and the metallic cations (*73*). This effect is unwarranted because the reduced bioavailability may render the antibiotic efficacy less effective. More importantly, the issue of bacterial resistance toward the antibiotic raises great concerns as it can leads to more serious diseases amongst the patients (*74*). Generally, the fluoroquinolone resistance is caused by chromosomal mutations in the bacterial topoisomerase II and IV (*74*).

The application of CFX in DDS is quite an active area, wherein the antibiotic has been incorporated into a number of different drug hosts. Amongst the previously reported drug hosts are cyclodextrin (*75*), chitosan/polyethylene glyocol (PEG) film (*76*), elastomeric device (*77*), PLGA microparticle (*78*) and polymeric nanoparticle (*79*).

Reports on the LMH materials intercalated with CFX have been made available by Lion et al. (*80*) and Hesse et al (*81*). In the former report, the antibiotic was intercalated in layered double hydroxides (LDH), a family of the LMH materials, via co-precipitation and anion exchange methods. However, the release property of the obtained intercalation compounds was not determined (*80*). For the latter report, a prostheses coated with CFX-intercalated LDH was prepared for treatment of recurring chronic otitis media. Interestingly, the CFX–LDH-coated prostheses showed excellent antimicrobial activity against *Pseudomonas aeruginosa* in rabbit ears. This study demonstrates for the first time the application of the CFX–LDH intercalation compound *in vivo*. However, the cytotoxicity study of the obtained compound was not performed (*81*).

As research in drug delivery systems continue to grow, there is a growing concern on the toxicity of the carrier candidates and the resulting host–drug complexes towards the human body (*15*, *82*). Studies have shown that nanomaterials such as silicate (*83*), silver (*84*), lipid nanoparticle (*85*), metal oxide (*86*) and graphene (*87*), among

others, cause toxic effects via various cellular interactions. The toxicity of the LMH hosts has been studied by a few groups (*88*, *89*) but similar work on the LMH–drug intercalation compounds are still lacking. It is worth to note that drug toxicity can be reduced when it is intercalated in the LMH hosts compared to when it is in the free from (*90, 91, 92*). Choy et al. has attributed the reduced toxicity to specific chemical interactions that occur between the intercalated drug and the hosts (*93*).

As we present above the backgrounds of ECA and CFX in DDS, especially concerning their prior relations with the LMH layered hosts, it occurred to us that there are two areas where research has been hitherto relatively lack; the release mechanisms which govern the release process of the intercalated drug and the toxicity study of the intercalation compound. This is based on our literature survey which reveals that most studies on LMH are rather concentrated on the synthesis and characterization aspects of the LMH–drug intercalation compounds (*94*). Therefore, in this study, these two lacking areas were given emphasis as we prepared a series of LMH-based drug hosts intercalated with the two drug models, ECA and CFX, in order to better understand the release process of the intercalated drugs from the layered hosts (*95*), as well as to establish the effect of the intercalation compounds toward the cells.

For the layered inorganic hosts, two prominent members of LMH, layered zinc hydroxides (LZH) and layered double hydroxides (LDH) are selected for hosting the model drugs, ECA and CFX. LZH and LDH, being the family members of LMH family share structural similarities with that of brucite, $[Mg(OH)_2]$ (*40*). However, their molecular structures differ in the chemical composition of the brucite-like lattice framework, where the LZH lattices consist of octahedral and tetrahedral zinc cations (Zn^{2+}), whereas divalent (Me^{2+}) and trivalent (Me^{3+}) metal cations constitute its sibling LDH lattices (*60*). The structural differences may lead to distinct chemistry, such as the in vitro release behavior between the sibling materials with the intercalated drug (*61*).

For the synthesis of intercalation compounds, co-precipitation is the preferred method over anion exchange due to the structural characters

of the host materials (*41*). It is proposed that any selected synthesis method may bestow a distinct orientation of guest molecules in the host interlayers and induce a different loading amount of the intercalated anion (*62)*. In this work, the obtained results from anion exchange and co-precipitation methods are compared especially in terms of the guest molecules orientation and spectroscopic measurements.

To complement our studies on the potentials of the LZH and LDH materials intercalated with CFX and ECA anions, cytotoxicity screenings are evaluated using African green monkey kidney (VERO) and human lung adenocarcinoma epithelial (A549) cell lines. Reports on drug–intercalated LMH compounds are widely available (*39, 42, 44, 63*) but cytotoxicity studies of the intercalation compound are relatively lacking (*64*).

1.3 **Objective of Research**

The objectives of this research are as follow:

1. To intercalate two relatively large drug molecules; namely ethacrynic acid (molecular weight 303.14 g/mol) and ciprofloxacin (molecular weight 331.34 g/mol) into the LZH and LDH host materials via anion exchange route and co-precipitation method.

2. To characterize the physico-chemical properties of the host materials, as well as the intercalation compounds using a broad range of characterization techniques such as powder X-ray diffraction (PXRD), Fourier transform infrared spectroscopy (FTIR), inductively coupled plasma-atomic absorption spectrophotometry (ICP–AES), Carbon, Hydrogen and Nitrogen analyses (CHN), thermogravimetric/differential thermogravimetric analysis (TG/DTG), surface area and porosity analysis (ASAP), scanning electron microscopy (SEM), transmission electron microscopy (TEM) and dynamic light scattering measurement (DLS).

3. To determine the release behavior of the intercalated drug molecules from their respective intercalation compounds upon

release in pH 6.0 and pH 7.4; being the pH of intestines and pH of blood, respectively.

4. To propose release mechanisms for the intercalation compounds based on the fitting of the release data using six kinetic models commonly used for the drug release; namely zeroth-order model, first-order model, parabolic diffusion model, modified Freundlich model, Elovich model and Bhaskar model.

5. To evaluate cytotoxicity profiles of the host materials and the intercalation compounds against VERO and A549 cell lines.

REFERENCES

1. National Nanotechnology Initiative. What is Nanotechnology. http://www.nano.gov/nanotech-101/what/definition (accessed Oct 16, 2013).

2. National Nanotechnology Initiative. What It Is and How It Works. http://www.nano.gov/nanotech-101/what (accessed Oct 16, 2013).

3. National Nanotechnology Initiative. Nanotechnology Timeline. http://www.nano.gov/timeline (accessed Oct 16, 2013).

4. E-drexler.com. K. Eric Drexler. http://e-drexler.com/p/idx04/00/0404drexlerBioCV.html (accessed Oct 16, 2013).

5. Kim, S.; Kwon, I. K.; Kwon, I. C.; Park, K. 2009. Nanotechnology in Drug Delivery: Past, Present, and Future. In *Nanotechnology in Drug Delivery;* Villiers, M. M., Aramnong, P., Kwon, G. S.; Eds.; Springer: New York, 2009; pp 581–596.

6. Farokhzad, O. C.; Langer, R. Impact of Nanotechnology on Drug Delivery. *ACS Nano*. **2009**, 3, 16–20.

7. Kim, D. K.; Dobson, J. Nanomedicine for Targeted Drug Delivery. *J. Mater. Chem*. **2009**, 19, 6294–6307.

8. Couvreur, P.; Gref, R.; Andrieux, K.; Malvy, C. Nanotechnologies for Drug Delivery: Application to Cancer and Autoimmune Diseases. *Progress in Solid State Chem*. **2006**, 34, 231–235.

9. Euliss, L. E.; DuPont, J. A.; Gratton, S.; DeSimone, J. Imparting Size, Shape, and Composition Control of Materials for Nanomedicine. *Chem. Soc. Rev*. **2006**, 35, 1095–1104.

10. Thanh, N. T. K.; Green, L. A. W. Functionalization of Nanoparticles for Biomedical Applications. *Nano Today*. **2010**, 5, 213–230.

11. Kawasaki, E. S.; Player, A. Nanotechnology, Nanomedicine, and the Development of New, Effective Therapies for Cancer. *Nanomed–Nanotechnol*. **2005**, 1, 101–109.

12. Vergoni, A. V.; Tosi, G.; Tacchi, R.; Vandelli, M. A.; Bertolini, A.; Costantino, L. Nanoparticles as Drug Delivery Agents Specific for CNS: *In Vivo* Biodistribution. *Nanomed–Nanotechnol.* **2009**, 5, 369–377.

13. Sokolova, V.; Epple. M. Inorganic Nanoparticles as Carriers of Nucleic Acids into Cells. *Angew. Chem. Int. Ed.* **2008**, 47, 1382–1395.

14. Williams, D. The Relationship between Biomaterials and Nanotechnology. *Biomaterials.* **2008**, 29, 1737–1738.

15. Nel, A.; Xia, T.; Madler, L.; Li, N. Toxic Potential of Materials at the Nanolevel. *Science.* **2006**, 311, 622–627.

16. Kohane, D. S.; Langer, R. Drug Delivery and Translation. *Drug Deliv. Transl. Res.* **2011**, 1, 4–6.

17. Jain, K. K. 2008. Drug Delivery Systems: An Overview. In *Methods in Molecular Biology;* Jain. K. K.; Ed.; Humana Press: New Jersey, 2008; pp 1–50.

18. Angelova, A.; Angelov, B.; Mutafchieva, R.; Lesieur, S.; Couvreur, P. Self-Assembled Multicompartment Liquid Crystalline Lipid Carriers for Protein, Peptide and Nucleic Acid Drug Delivery. *Acc. Chem. Res.* **2011**, 44, 147–156.

19. Nanda, R.; Sasmal, A.; Nayak, P. L. Preparation and Characterization of Chitosan–Polylactide Composites Blended with Cloisite 30B for Controlled Release of the Anticancer Drug Paclitaxel. *Carbohyd. Polym.* **2011**, 83, 988–994.

20. Ruiz-Hitzky, E.; Darder, M.; Aranda, P.; del Burgo, M. A. M.; del Real, G. Bionanocomposites as New Carriers for Influenza Vaccines. *Adv. Mater.* **2009**, 21, 4167–4171.

21. Choy, J. H.; Kwak, S. Y.; Park, J. S.; Jeong, Y. J.; Portier. J. Intercalative Nanohybrids of Nucleoside Monophosphates and DNA in Layered Metal Hydroxide. *J. Am. Chem. Soc.* **1999**, 121, 1399–1400.

22. Allen, T. M.; Cullis, P. R. Drug Delivery Systems: Entering the Mainstream. *Science.* **2004**, 303, 1818–1822.

23. Hubbell, J. A. Enhancing Drug Function. *Science*. **2003**, 300, 595–596.

24. Zahr, A. S.; Pishko. M. V. Nanotechnology for Cancer Chemotherapy. In *Nanotechnology in Drug Delivery*; Villiers, M. M., Aramnong, P., Kwon, G. S.; Eds.; Springer: New York, 2009; pp 491–518.

25. Hoffman, A. S. The Origins and Evolution of "Controlled" Drug Delivery Systems. *J. Control. Release*. **2008**, 132, 153–163.

26. Sahoo, S. K.; Jain, T. K.; Reddy, M. K.; Labhasetwar, V. 2010. Nano-Sized Carriers for Drug Delivery. In *NanoBioTechonology: BioInspired Devices and Materials of the Future*; Shoseyov, O., Levy, I.; Eds.; Humana Press: 2010; pp 329–348.

27. Park, C.; Youn, H.; Kim, H.; Noh, T.; Kook, Y. H.; Oh, E. T.; Park, H. J.; Kim, C. Cyclodextrin-covered Gold Nanoparticles for Targeted Delivery of an Anti-Cancer Drug. *J. Mater. Chem.* **2009**, 19, 2310–2315.

28. Leroux, J. C.; Allemann, E.; Jaeghere, F. D.; Doelker, E.; Gurny, R. Biodegradable Nanoparticles: From Sustained Release Formulations to Improved Site Specific Drug Delivery. *J. Control Release*. **1996**, 39, 339-350.

29. Fadeel, B.; Garcia-Bennett, A. E. Better Safe than Sorry: Understanding the Toxicological Properties of Inorganic Nanoparticles Manufactured for Biomedical Applications. *Adv. Drug Deliver. Rev*. **2010**, 62, 362–374.

30. Yoon, H. J.; Jang, W. D. Polymeric Supramolecular Systems for Drug Delivery. *J. Mater. Chem*. **2010**, 20, 211–222.

31. Chandra, S.; Mehta, S.; Nigam, S.; D. Bahadur. Dendritic Magnetite Nanocarriers for Drug Delivery Applications. *New J. Chem*. **2010**, 34, 648–655.

32. Zhou. Y. Lipid Nanotubes: Formation, Templating Nanostructures and Drug Nanocarriers. *Crit. Rev. Solid State*. **2008**. 183–196.

33. Boisselier, E.; Didier Astruc, D. Gold Nanoparticles in Nanomedicine: Preparations, Imaging, Diagnostics, Therapies and Toxicity. *Chem. Soc. Rev*. **2009,** 38, 1759–1782.

34. Manzano, M.; Vallet-Regi, M. New Developments in Ordered Mesoporous Materials for Drug Delivery. *J. Mater. Chem*. **2010**, 20, 5593–5604.

35. Oh, J. M.; Choi, S. J.; Lee, G. E.; Han, S. H.; Choy. J. H. Inorganic Drug-Delivery Nanovehicle Conjugated with Cancer-Cell-Specific Ligand. *Adv. Funct. Mater*. **2009**, 19, 1617–1624.

36. Ruiz-Hitzky, E.; Darder, M.; Aranda, P. Functional Biopolymer Nanocomposites Based on Layered Solids. *J. Mater. Chem*. **2005**, 15, 3650–3662.

37. Cygan, R. T.; Greathouse, J. A.; Heinz, H.; Kalinichev, A. G. Molecular Models and Simulations of Layered Materials. *J. Mater. Chem*. **2009**, 19, 2470–2481.

38. Utracki, L. A.; Sepehr, M.; Boccaleri, E. Synthetic, Layered Nanoparticles for Polymeric Nanocomposites (PNCs). *Polym. Adv. Technol*. **2007**, 18, 1–37.

39. Oh, J. M.; Biswick, T. T.; Choy, J. H. Layered Nanomaterials for Green Materials. *J. Mater. Chem*. **2009**, 19, 2553–2563.

40. Evans, D. G.; Slade, R. C. T. 2006. Structural Aspects of Layered Double Hydroxides. In *Layered Double Hydroxides*; Duan, X., Evans, D. G.; Eds.; Springer: Berlin, 2006; pp 1–87.

41. Cavani, F.; Trifir, F.; Vaccari, A. Hydrotalcite–type Anionic Clays: Preparation, Properties and Applications. *Catal. Today*. **1991**, 11, 173–301.

42. Rives, V.; del Arco, M.; Martín. C. Layered Double Hydroxides as Drug Carriers and for Controlled Release of Non-Steroidal Antiinflammatory Drugs (NSAIDs): A Review. *J. Control. Release*. **2013**, 169, 28–39.

43. Costantino, U.; Ambrogi, V.; Nocchetti, M.; Perioli, L. Hydrotalcite-like Compounds: Versatile Layered Hosts of Molecular Anions with Biological Activity. *Micropor. Mesopor. Mat.* **2008**, 107, 149–160.

44. Xu, Z. P.; Lu, G. Q. Layered Double Hydroxide Nanomaterials as Potential Cellular Drug Delivery Agents. *Pure Appl. Chem.* **2006**, 78, 1771–1779.

45. Gunawan, P.; Xu, R. Direct Control of Drug Release Behavior from Layered Double Hydroxides Through Particle Interactions. *J. Pharm. Sci.* **2008**, 97, 4367–4378.

46. del Arco, M.; Gutierrez, S.; Cristina Martin, C.; Rives, V.; Rocha, J. Synthesis and Characterization of Layered Double Hydroxides (LDH) Intercalated with Non-Steroidal Anti-Inflammatory Drugs (NSAID). *J. Solid State Chem.* **2004**, 177, 3954–3962.

47. Chakraborty, M.; Dasgupta, S.; Sengupta, S.; Chakraborty, J.; Ghosh, S.; Ghosh, J.; Mitra, M. K.; Mishra, A.; Mandal, T. K.; Basu, D. A Facile Synthetic Strategy for Mg–Al Layered Double Hydroxide Material as Nanocarrier for Methotrexate. *Ceram. Int.* **2012**, 38, 941–949.

48. Pan, D.; Zhang, H.; Zhang, T.; Duan, X. A Novel Organic–Inorganic Microhybrids Containing Anticancer Agent Doxifluridine and Layered Double Hydroxides: Structure and Controlled Release Properties. *Chem. Eng. Sci.* **2010**, 65, 3762–3771.

49. Panda, H. S.; R. Srivastava, R.; Bahadur, D. In-Vitro Release Kinetics and Stability of Anticardiovascular Drugs-Intercalated Layered Double Hydroxide Nanohybrids. *J. Phys. Chem. B.* **2009**, 113, 15090–15100.

50. Wang, J.; Liu, Q.; Zhang, G.; Li, Z.; Yang, P.; Jing, X.; Zhanga, M.; Liu, T.; Jiang, Z.; Synthesis, Sustained Release Properties of Magnetically Functionalized Organic–Inorganic Materials: Amoxicillin Anions Intercalated Magnetic Layered Double Hydroxides via Calcined Precursors at Room Temperature. *Solid State Sci.* **2009**, 11, 1597–1601.

51. Trikeriotis, M.; Ghanotakis, D. F. Intercalation of Hydrophilic and Hydrophobic Antibiotics in Layered Double Hydroxides. *Int. J. Pharm.* **2007**, 332, 176–184.

52. Zhang, H.; Zou, K.; Guo, S.; Duan. X. Nanostructural Drug-Inorganic Clay Composites: Structure, Thermal Property and In Vitro Release of Captopril-Intercalated Mg–Al–Layered Double Hydroxides. *J. Solid State Chem.* **2006**, 179, 1792–1801.

53. Kleit, S. A.; Hamburger, R. J.; Martz, B. L.; Fisch, C. Fundamentals of Clinical Cardiology. *Am. Heart J.* **1970**, 79, 700-712.

54. Cannon, P. J.; Kilcoyne, M. M. Ethacrynic Acid and Furosemide: Renal Pharmacology and Clinical Use. *Prog. Cardiovac. Dis.* **1969**, 12, 99-1118.

55. Lang, H. J.; Hroport, M. Discovery and Development of Diuretic Agents. In Handbook of Experimental Pharmacology: Volume 117: Diuretics; Greger, R. F.; Knauf, H.; Mutschler, E.; Eds.; Springer-Verlag: Berlin, 1995; pp 141-172.

56. Cynkowska, G.; Cynkowski, T.; Al-Ghananeem, A. A.; Guo, H.; Ashton, P.; Crooks, P. A. Novel Antiglaucoma Prodrugs and Codrugs of Ethacrynic Acid. *Bioorgan. Med. Chem. Lett.* **2005**, 15, 3524-3527.

57. Aizawa, S.; Ookawa, K.; Kudo, T.; Asano, J.; Hayakari, M.; Tsuchida, S. Characterization of Cell Death Induced by Ethacrynic Acid in a Human Colon Cancer Cell Line DLD-1 and Suppression by N-acetyl-L-cysteine. *Cancer Sci.* **2003**, 94, 886-893.

58. Tew, K. D.; Bomber, A. M.; Hoffman, S. J. Ethacrynic Acid and Piriprost as Enhancers of Cytotoxicity in Drug Resistant and Sensitive Cell Lines. *Cancer Res.* **1988**, 48, 3622-3625.

59. Somberg, J. C.; Molnar, J. The Pleiotropic Effects of Ethacrynic Acid. *Am. J. Ther.* **2009**, 16, 102–104.

60. Cannon, P. J.; Heinemann, H. O.; Stason, W. B.; Laragh, J. Ethacrynic Acid: Effectiveness and Mode of Diuretic Action in Man. *Circulation.* **1965**, 16, 4-18.

61. Cooperman, L. B.; Rubin I. L. Toxicity of Ethacrynic Acid and Furosemide. *Am. J. Ther*. **1973**, 85, 831-834.

62. Gaudan, R.; Jwala, J.; Boddu, S. H. S.; Mitra, A. K. Recent Perspectives in Ocular Drug Delivery. *Pharm. Res*. **2009**, 26, 1197-1216.

63. Kalish, R. S.; Wood, J. A.; Kydonieus, A.; Wille, J. J. Prevention of Contact Hypersensitivity to Topically Applied Drugs by Ethacrynic Acid: Potential Application to Transdermal Drug Delivery. *J. Control. Release*. **1997**, 48, 79–87.

64. Wang, Y.; Challa, P.; Epstein, D. L.; Yuan, F. Controlled Release of Ethacrynic Acid from Poly(Lactide-co-Glycolide) Films for Glaucoma Treatment. *Biomaterials*. **2004**, 25, 4279–4285.

65. Kim, J. Y.; Choi, S. J.; Oh, J. M.; Park, T.; Choy, J. H. Anticancer Drug-Inorganic Nanohybrid and Its Cellular Interaction. *J. Nanosci. Nanotechno*. **2007**, 7, 3700–3705.

66. Ladewig, K.; Niebert, M.; Xu, Z. P.; Gray, P. P.; Lu, G. Q. Efficient siRNA Delivery to Mammalian Cells using Layered Double Hydroxide Nanoparticles. *Biomaterials*, **2010**, 31, 1821–829.

67. Gu, Z.; Rolfe, B. E.; Xu, Z. P.; Thomas, A. C.; Campbell, J. H.; Lu, G. Q. M. Enhanced Effects of Low Molecular Weight Heparin Intercalated with Layered Double Hydroxide Nano Particles on Rat Vascular Smooth Muscle Cells. *Biomaterials*. **2010**, 31, 5455-5462.

68. Khan, A. I.; Ragavan, A.; Fong, B.; Markland, C.; O'Brien, M.; Dunbar, T. G.; Williams, G. R.; O'Hare. D. Recent Developments in the Use of Layered Double Hydroxides as Host Materials for the Storage and Triggered Release of Functional Anions. *Ind. Eng. Chem. Res*. **2009**, 48, 10196–10205.

69. Jeong, Y. I,; Na, H. S.; Seo, D. H.; Kim, D. G.; Lee, H. C.; Jang, M. K.; Na, S. K.; Roh, S. H.; Kim, S. I.; Nah, J. W. Ciprofloxacin-encapsulated Poly(DL-lactide-co-glycolide) Nanoparticles and Its Antibacterial Activity. *Int. J. Pharm.* **2008**, 352, 317–323.

70. Zhanel, G. G.; Ennis, K.; Vercaigne, L.; Walkty, A.; Gin, A. S.; Embil, J.; Smith, H.; Hoban, D. J. A Critical Review of the Fluoroquinolones: Focus on Respiratory Tract Infections. *Drugs*. **2002,** 62, 13-59.

71. Ball, P. 2000. The Quinolones: History and Overview. In *The Quinolones: Third Edition*; Andriole, V. T.; Ed.; Academic Press: California, 2000; pp 1–31.

72. Köhler, T.; Pechère, J. C. 2000. Bacterial Resistance to Quinolones: Mechanisms and Clinical Implications. In *The Quinolones: Third Edition*; Andriole, V. T.; Ed.; Academic Press: California, 2000; pp 139–167.

73. Blanchemain, N., Karrout, Y.; N. Tabary, N.; M. Bria, M.; Neuta, C.; Hildebrand, H. F.; Siepmann, J.; Martel, B. Comparative Study of Vascular Prostheses Coated with Polycyclodextrins for Controlled Ciprofloxacin Release. *Carbohyd. Polym.* **2012**, 90, 1695–1703.

74. Wang, Q.; Dong, Z.; Du, Y.; Kennedy, J. F. Controlled release of Ciprofloxacin Hydrochloride from Chitosan/Polyethylene Glycol Blend Films. *Carbohyd. Polym*. **2007**, 69, 336–343.

75. Tobias, I. S.; Lee, H.; Engelmayr Jr., G.; Macaya, D.; Bettinger, C.; Cima, M.. Zero-order Controlled Release of Ciprofloxacin-HCl from a Reservoir-based, Bioresorbable and Elastomeric Device. *J. Control. Rel*. **2010**, 46, 356-362.

76. Bhaskar, R.; Murthy, R.S.R.; Miglani, B.D.; Viswanathan. K. Novel Method to Evaluate Diffusion Controlled Release of Drug from Resinate. *Int. J. Pharm*. **1986**, 28, 59-66.

77. Paul. D. R. Elaborations on the Higuchi Model for Drug Delivery. *Int. J. Pharm*. **2011**, 418, 13–17.

78. Rothstein, S. N.; Little, S. R. A "Tool Box" for Rational Design of Degradable Controlled Release Formulations. *J. Mater. Chem.* **2011**, 21, 29–39.

79. Lao, L. L.; Peppas, N. A.; Boey, F. Y. C.; Venkatraman, S. S. Modeling of Drug Release from Bulk-Degrading Polymers. *Int. J. Pharm.* **2011**, 418, 28–41.

80. Rothstein, S. N.; Federspiel, W. J.; Little, S. R. A Simple Model Framework for the Prediction of Controlled Release from Bulk Eroding Polymer Matrices. *J. Mater. Chem.* **2008**, 18, 1873–1880.

81. Singh, M.; Janice A. Lumpkin, J. A.; Joel Rosenblatt, J. Mathematical Modeling of Drug Release from Hydrogel Matrices via a Diffusion Coupled with Desorption Mechanism. *J. Control. Release*. **1994**, 32, 17–25.

82. Zhang, X.; Wyss, U. P.; Pichora, D.; Goosen, M. F. A. A Mechanistic Study of Antibiotic Release from Biodegradable Poly(D, L-Lactide) Cylinders. *J. Control. Release*. **1994**, 31, 129–144.

83. Lee, P. I. Kinetics of Drug Release from Hydrogel Matrices. *J. Control. Release*. **1985**, 2, 277–288.

84. Li, Z. Sorption Kinetics of Hexadecyltrimethylammonium on Natural Clinoptilolite. *Langmuir*, **1999**, 15, 6438–6445.

85. Sharpley, A. N. Effect of Soil Properties on the Kinetics of Phosphorus Desorption. *Soil Sci. Soc. Am. J.* **1983**, 47, 462–467.

86. Siepmann, J.; Peppas, N. A. Higuchi Equation: Derivation, Applications, Use and Misuse. *Int. J. Pharm.* **2011**, 418, 6–12.

87. Choi, S. J.; Choy, J. H. Effect of Physico-Chemical Parameters on the Toxicity of Inorganic Nanoparticles. *J. Mater. Chem.* **2011**, 21, 5547–5554.

88. Sahay, G.; Alakhova, D. Y.; Kabanov. A. V. Endocytosis of Nanomedicines. *J. Control. Release*. **2010**, 145, 182–195.

89. Oh, J. M.; Choi, S. J.; Go-Eun Lee, G. E.; Kim, J. E.; Choy, J. H. Inorganic Metal Hydroxide Nanoparticles for Targeted Cellular Uptake through Clathrin-Mediated Endocytosis. *Chem. Asian J.* **2009**, 4, 67 – 73.

90. Nowacek, A. S.; Balkundi, S.; McMillan J.; Roy, U.; Martinez-Skinner, A.; Lee Mosley, R.; Kanmogne, G.; Kabanov, A. V.; Bronich, T.; Gendelman, H. E. Analyses of Nanoformulated Antiretroviral Drug Charge, Size, Shape and Content for Uptake, Drug Release and Antiviral Activities in Human Monocyte-Derived Macrophages. *J. Control. Release*. **2011**, 150, 204–211.

91. Herrero, M.; Labajos, F. M.; Rives. V. Size Control and Optimisation of Intercalated Layered Double Hydroxides. *Appl. Clay Sci.* **2009**, 2, 510–518.

92. Xu, Z. P.; Stevenson, G.; Lu, C. Q.; Lu. G. Q. Dispersion and Size Control of Layered Double Hydroxide Nanoparticles in Aqueous Solutions. *J. Phys. Chem. B.* **2006**, 110, 16923-16929.

93. Brandhonneur, N.; Chevanne, F.; Vie, V.; Frisch, B.; Primault, R.; Le Potier, M. F.; Le Corre, P. Specific and Non-Specific Phagocytosis of Ligand-Grafted PLGA Microspheres by Macrophages. *European J. Pharm. Sci.* **2009**, 36, 474–485.

94. Kaminskas, L. M.; Kelly, B. D.; McLeod, V. M.; Sberna,G.; Boyd, B. J.; Owen, D. J.; Porter. C. J. H. Capping Methotrexate α-Carboxyl Groups Enhances Systemic Exposure and Retains the Cytotoxicity of Drug Conjugated PEGylated Polylysine Dendrimers. *Mol. Pharmaceutics*, **2011**, 8, 338–349.

95. Zhu, L.; Ma, J.; Jia, N.; Zhao, Y.; Shen. H. Chitosan-Coated Magnetic Nanoparticles as Carriers of 5-Fluorouracil: Preparation, Characterization and Cytotoxicity Studies. *Colloid. Surface B.* **2006**, 68, 1–6.

96. Chairam, S.; Somsook, E. Starch Vermicelli Template for Synthesis of Magnetic Iron Oxide Nanoclusters. *J. Magn. Magn. Mate*r. **2008**, 320, 2039–2043.

97. Park, J.; Fong, P. M.; Lu, J.; Russell, K. S.; Booth, C. J.; Saltzman, W. M.; Fahmy, T. M. PEGylated PLGA Nanoparticles for the Improved Delivery of Doxorubicin. *Nanomed–Nanotechnol.* **2009**, 5, 410–418.

98. Pastorin, G.; Wu, W.; Wieckowski, S.; Briand, J. P.; Kostarelos, K.; Prato, M.; Bianco. A. Double Functionalisation of Carbon Nanotubes for Multimodal Drug Delivery. *Chem. Commun.* **2006**, 1182–1184.

99. Sunoqrot, S.; Bae, J. W.; Jin, S. E.;Pearson, R. M.; Liu, Y.; Hong, S. Kinetically Controlled Cellular Interactions of Polymer-Polymer and Polymer-Liposome Nanohybrid Systems. Bioconjugate Chem. 2011, 22, 466–474.

100. George, S.;Pokhrel, S.; Xia, T.; Gilbert, B.; Ji, Z.; Schowalter, M.; Rosenauer, A.; Damoiseaux, R.; Bradley, K. A.; Madler, L.; Nel, A. E. Use of a Rapid Cytotoxicity Screening Approach to Engineer a Safer Zinc Oxide Nanoparticle through Iron Doping. *ACS Nano.* **2010**, 4, 15–29.

101. Aryal, B. P.; Neupane, K. P.; Sandros, M. G.; Benson, D. E. Metallothioneins Initiate Semiconducting Nanoparticle Cellular Toxicity. *Small.* **2006**, 2, 1159–1163.

102. Casals, E.; Vazquez-Campos, S.; Bastus, N. G.; Puntes, V. Distribution and Potential Toxicity of Engineered Inorganic Nanoparticles and Carbon Nanostructures in Biological Systems. *Trac-Trend. Anal. Chem.* **2008**, 27, 672–683.

103. Gil, P. R.; Oberdorster, G.; Elder, A.; Puntes, V.; Parak. W. J. Correlating Physico-Chemical with Toxicological Properties of Nanoparticles: The Present and the Future. *ACS Nano.* **2010**, 4, 5527–5531.

104. Massich, M. D.; Giljohann, D. A.; Schmucker, A. L.; Patel, P. C.; Mirkin, C. A. Cellular Response of Polyvalent Oligonucleotide Gold Nanoparticle Conjugates. *ACS Nano.* **2010**, 4, 5641–5646.

105. Araujo, J.; Gonzalez, E.; Egea, M. A.; Garcia, M. L.; Souto. E. B. Nanomedicines for Ocular NSAIDs: Safety on Drug Delivery. *Nanomed–Nanotechnol.* **2009**, 5, 394–401.

106. Cao, Z.; Yu, Q.; Xue, H.; Cheng, G.; Jiang. S. Nanoparticles for Drug Delivery Prepared from Amphiphilic PLGA Zwitterionic Block Copolymers with Sharp Contrast in Polarity between Two Blocks. *Angew. Chem. Int. Ed.* **2010**, 49, 3771–3776.

107. Zhu, R.; Jiang, W.; Pu, Y.; Luo, K.; Wu, Y.; He, B.; Gu. Z. Functionalization of Magnetic Nanoparticles with Peptide Dendrimers. *J. Mater. Chem.* **2011**, 21, 5464–5474.

108. Feng, S. S.; Mei, L.; Anitha, P.; Gan, C. W.; Zhou, W. Poly(Lactide)–Vitamin E Derivative/Montmorillonite Nanoparticle Formulations for the Oral Delivery of Docetaxel. *Biomaterials*, **2009**, 30, 3297–3306.

109. Figueras, F. 2010. Basicity, Catalytic and Adsorptive Properties of Hydrotalcites. In *Pillared Clays and Related Catalysts*; Gil, A., Korili, S. A., Trujillano, R., Vicente, M. A.; Eds.; Springer: New York. 2010; pp 399–422.

110. Darder, M.; Aranda, P.; Ruiz-Hitzky, E. Bionanocomposites: A New Concept of Ecological, Bioinspired, and Functional Hybrid Materials. *Adv. Mater.* **2007**, 19, 1309–1319.

111. Fogg, A. M.; Green, V. M.; Harvey, H. G.; O'Hare, D. New Separation Science Using Shape-Selective Ion Exchange Intercalation Chemistry. *Adv. Mater.* **1999**, 11, 1466–1469.

112. Williams, G. R.; O'Hare, D. Towards Understanding, Control and Application of Layered Double Hydroxide Chemistry. *J. Mater. Chem.* **2006**, 16, 3065–3074.

113. Newman, S. P.; Jones, W. Comparative Study of Some Layered Hydroxide Salts Containing Exchangeable Interlayer Anions. *J. Solid State Chem.* **1999**, 148, 26–40.

114. Benard, P.; Auffredic, J. P.; D. Louer. D. A Study of the Thermal Decomposition of Ammine Zinc Hydroxide Nitrates. *Thermochim. Acta.* **1994**, 232, 65–76.

115. Stahlin, W.; Oswald, H. R. The Infrared Spectrum and Thermal Analysis of Zinc Hydroxide Nitrate. *J. Solid State Chem.* **1971**, 2, 252–255.

116. Arizaga, G. G. C.; Gardolinski, J. E. F. C.; Schreiner, W. H.; Wypych, F. Intercalation of an Oxalatooxoniobate Complex into Layered Double Hydroxide and Layered Zinc Hydroxide Nitrate. *J. Colloid Interf. Sci.* **2009**, 330 352–358.

117. Cursino, A. C. T.; Gardolinski, J. E. F. C.; Wypych, F. Intercalation of Anionic Organic Ultraviolet Ray Absorbers into Layered Zinc Hydroxide Nitrate. *J. Colloid Interf. Sci.* **2010**, 347, 49–55.

118. Rocca, E.; Caillet, C.; Mesbah, A.; Francois, M.; Steinmetz, J. Intercalation in Zinc-Layered Hydroxide: Zinc Hydroxyheptanoate Used as Protective Material on Zinc. *Chem. Mater.* **2006**, 18, 6186–6193.

119. Eriksson, L.; Louer, D.; Werner, P. E. Crystal Structure Determination and Rietveld Refinement of $Zn(OH)(NO_3).H_2O$. *J. Solid State Chem.* **1989**, 81, 9–20.

120. Zhang, W.; Yanagisawa, K. Hydrothermal Synthesis of Zinc Hydroxide Chloride Sheets and Their Conversion to ZnO. *Chem. Mater.* **2007**, 19, 2329–2334.

121. Poul, L.; Jouini, N.; Fievet, F. Layered Hydroxide Metal Acetates (Metal = Zinc, Cobalt, and Nickel): Elaboration via Hydrolysis in Polyol Medium and Comparative Study. *Chem. Mater.* **2000**, 12, 3123–3132.

122. Kasai, A.; Fujihara, S. Layered Single-Metal Hydroxide/Ethylene Glycol as a New Class of Hybrid Material. *Inorg. Chem.* **2006**, 45, 415−418.

123. Tagaya, H.; Sasaki, N.; Morioka, H.; Kadokawa, J. Preparation of New Inorganic−Organic Layered Compounds, Hydroxy Double Salts, and Preferential Intercalation of Organic Carboxylic Acids into Them. *Mol. Cryst. Liq. Cryst.* **2000**, 341, 413−418.

124. Biswick, T.; Jones, W.; Pacula, A.; Serwicka, E. Synthesis, Characterisation and Anion Exchange Properties of Copper, Magnesium, Zinc and Nickel Hydroxy Nitrates. *J. Solid State Chem.* **2006**, 179, 49–55.

125. Arizaga, G. C. C.; Mangrich, A. S.; Gardolinski, J. E. F. C.; Wypych, F. Chemical Modification of Zinc Hydroxide Nitrate and Zn–Al-Layered Double Hydroxide with Dicarboxylic Acids *J. Colloid Interf. Sci.* **2008**, 320, 168–176.

126. Tronto, J.; Leroux, F.; Dubois, M.; Taviot-Gueho, C.; Valim, J. B. Hybrid Organic–Inorganic Materials: Layered Hydroxy Double Salts Intercalated with Substituted Thiophene Monomers. *J. Phys. Chem. Solid*s. **200**6, 67, 978–982.

127. Arizaga, G. G. C.; Schreiner, W. H.; Wypych, F. Intercalation of an Oxalatooxoniobate Complex into Layered Double Hydroxide and Layered Zinc Hydroxide Nitrate. . *J. Colloid Interf. Sci.* **2009**, 330, 352–358.

128. Demel, J.; Kubat, P.; Jirka, I.; Kovar, P.; Pospisil, M.; Lang, K. Inorganic-Organic Hybrid Materials: Layered Zinc Hydroxide Salts with Intercalated Porphyrin Sensitizers. *J. Phys. Chem. C*. **2010**, 114, 16321–16328.

129. Hussein, M. Z.; Ghotbi, M. Y.; Yahaya, A.; Abd Rahman, M. Z. Synthesis and Characterization of (Zinc-Layered-Gallate) Nanohybrid using Structural Memory Effect. *Mater. Chem. Phys*. **2009**, 113, 491–496.

130. He, J.; Wei, M.; Li, B.; Kang, Y.; Evans, D. G.; Duan, X. Preparation of Layered Double Hydroxides. In *Layered Double Hydroxides*; Duan, X., Evans, D. G.; Eds., Springer–Verlag: Berlin, 2006, pp 90–119.

131. Newman, S. P.; William Jones, W. Synthesis, Characterization and Applications of Layered Double Hydroxides Containing Organic Guests. *New J. Chem*. **1998**, 22, 105–115.

132. Li, F.; Duan, X. 2006. Applications of Layered Double Hydroxides. In *Layered Double Hydroxides*; Duan, X., Evans, D. G.; Eds.; Springer: Berlin, 2006, pp 193–223.

133. Khan, A. I.; Lei, L.; Norquist, A.J.; O'Hare, D. Intercalation and Controlled Release of Pharmaceutically Active Compounds from A Layered Double Hydroxide. *Chem. Commun*. **2001**, 2342–2343.

134. Choy, J. H.; Park, M.; Oh, J. M. 2008. Gene and Drug Delivery System with Soluble Inorganic Carriers. In *NanoBioTechnology: BioInspired Devices and Materials of the Future*; Shoseyov, O., Levy. I.; Eds.; Humana Press: New Jersey, 2008, pp 347–369.

135. Rojas, R.; Palena, M.C.; Jimenez-Kairuz, A.F.; Manzo, R.H.; Giacomelli, C.E. Modeling Drug Release from a Layered Double Hydroxide–Ibuprofen Complex. *Appl. Clay Sci.* **2012**, 62–63, 15–20.

136. Abdul Latip, A. F.; Hussein, M. Z.; Stanslas, J.; Wong, C. C.; Adnan, R. Release Behavior and Toxicity Profiles towards A549 Cell Lines of Ciprofloxacin From Its Layered Zinc Hydroxide Intercalation Compound. *Chem. Centr. J.* **2013**, 7, 119–129.

137. Perioli, L.; T. Posati, T.; M. Nocchetti, M.; Bellezza, F.; Costantino, U.; Cipiciani. A. Intercalation and Release of Antiinflammatory Drug Diclofenac into Nanosized ZnAl Hydrotalcite-Like Compound. *Appl. Clay Sci.* **2011**, 53, 374–378.

138. Berber, M. R.; Minagawa, K.; Katoh, M; Mori, T.; Tanaka, M. Nanocomposites of 2-Arylpropionic Acid Drugs Based on Mg–Al Layered Double Hydroxide for Dissolution Enhancement. *Eur. J. Pharm.Sci.* **2008**, 35, 354–360.

139. San Roman, M. S.; Holgado, M J.; Salinas, B.; Rives, V. Characterisation of Diclofenac, Ketoprofen or Chloramphenicol Succinate Encapsulated in Layered Double Hydroxides with the Hydrotalcite-Type Structure. *Appl. Clay Sci.* **2012**, 55, 158–163.

140. del Arco, M.; Fernández, A.; Martín, C.; Rives, V. Release Studies of Different NSAIDs Encapsulated in Mg,Al,Fe-Hydrotalcites. *Appl. Clay Sci.* **2009**, 42, 538–544.

141. Alcantara, A. C. S.; Aranda, P.; Darder, M.; Ruiz-Hitzky, E. Bionanocomposites based on Alginate–Zein/Layered Double Hydroxide Materials as Drug Delivery Systems. *J. Mater. Chem.* **2010,** 20, 9495–9504.

142. DeLeon, V. H.; Thanh D. Nguyen, T. D.; Nar, M.; Nandika A. D'Souza, N. A.; Teresa D. Golden, T. D. Polymer Nanocomposites for Improved Drug Delivery Efficiency. *Mater. Chem. Phys.* **2012**, 132, 409–415.

143. Huh, A. J.; Kwon, Y. K. "Nanoantibiotics": A New Paradigm for Treating Infectious Diseases using Nanomaterials in the Antibiotics Resistant Era. *J. Control. Release.* **2011**, 156, 128–145.

144. Trikeriotis, M.; Ghanotakis, D. F. Intercalation of Hydrophilic and Hydrophobic Antibiotics in Layered Double Hydroxides. *Int. J. Pharm.* **2007**, 332, 176–184.

145. Wang, J.; Liu, Q.; Zhang, G.; Li, Z.; Yang, P.; Jing, X.; Zhang, M.; Liu, T.; Jiang, Z.; Synthesis, Sustained Release Properties of Magnetically Functionalized Organic–Inorganic Materials: Amoxicillin Anions Intercalated Magnetic Layered Double Hydroxides via Calcined Precursors at Room Temperature. *Solid State Sci.* **2009**, 11, 1597–1601.

146. Wang, Y.; Zhang, D. Synthesis, Characterization and Controlled Release Antibacterial Behavior of Antibiotic Intercalated Mg–Al Layered Double Hydroxides. *Mater. Res. Bull.* **2012**, 47, 3185–3194.

147. Ryu, S. J.; Jung, H.; Oh, J. M.; Lee, J. K.; Choy, J. H.; Layered Double Hydroxide as Novel Antibacterial Drug Delivery System. *J. Phys. Chem. Solids*. **2010**, 71, 685–688.

148. Tsung, J.; Burgess, D. J. 2012. Biodegradable Polymers in Drug Delivery Systems. In *Fundamentals and Applications of Controlled Release Drug Delivery*; Siepmann, J., Ronald, A. Siegel, R. A., Rathbone, M. J.; Eds.; Controlled Release Society: New York, 2012; pp 107–123.

149. Alexis, F.; Pridgen, E. M.; Langer, R., Farokhzad, O. C. 2010. Nanoparticle Technologies for Cancer Therapy. In *Drug Delivery*; Schafer-Korting, M.; Ed.; Springer: Heidelberg, 2010, pp 55–86.

150. Choy, J. H.; Jung, J. S.; Oh, J. M.; Park, M.; Jeong, J.; Kang, Y. K.; Han, O. K.; Layered Double Hydroxide as an Efficient Drug Reservoir for Folate Derivatives. *Biomaterials*. **2004**, 25, 3059–3064.

151. Choi, S. J.; Oh, J. M.; Choy, J. H. Anticancer Drug-Layered Hydroxide Nanohybrids as Potent Cancer Chemotherapy Agents. *J. Phys. Chem. Solids*. **2008**, 69, 1528–1532.

152. Choi, G.; Kim, S. Y.; Oh, J. M.; Choy, J. H. Drug-Ceramic 2-Dimensional Nanoassemblies for Drug Delivery System in Physiological Condition. *J. Am. Ceram. Soc.* **2012**, 95, 2758–2765.

153. Kim, J. Y.; Choi, S. J.; Oh, J. M.; Park, T.; Choy, J. H. Anticancer Drug-Inorganic Nanohybrid and Its Cellular Interaction. *J. Nanosci. Nanotechno.* **2007**, 7, 3700–3705.

154. Pan, D.; Zhang, H.; Zhang, T.; Duan, X. A Novel Organic–Inorganic Microhybrids Containing Anticancer Agent Doxifluridine and Layered Double Hydroxides: Structure and Controlled Release Properties. *Chem. Eng. Sci.* **2010**, 65, 3762–3771.

155. Li, F.; Jin, L.; Han, J.; Wei, M.; L, C. Synthesis and Controlled Release Properties of Prednisone Intercalated Mg-Al Layered Double Hydroxide Composite. *Ind. Eng. Chem. Res.* **2009**, 48, 5590–5597.

156. Biswick, T.; Park, D. H.; Shul, Y. G.; Choy, J. H. *p*-coumaric Acid–Zinc Basic Salt Nanohybrid for Controlled Release and Sustained Antioxidant Activity. *J. Phys. Chem. Solids.* **2010**, 71, 647–649.

157. Hussein, M. Z.; Al Ali, S. H.; Zainal, Z.; Hakim, M. N. Development of Antiproliferative Nanohybrid Compound with Controlled Release Property using Ellagic Acid as the Active Agent. *Int. J. Nanomed.* ***2011****, 6, 1373–1383.*

158. Al Ali, S. H. H.; Al-Qubaisi, M.; Hussein, M. Z.; Zainal, Z.; Hakim, M. N. Preparation of Hippurate-Zinc Layered Hydroxide Nanohybrid and Its Synergistic Effect with Tamoxifen on Hepg2 Cell Lines. *Int. J. Nanomed.* **2011**, 6, 3099–3111.

159. Choi, S. J.; Oh, J. M.; Choy, J. H. Human-Related Application and Nanotoxicology of Inorganic Particles: Complementary Aspects. *J. Mater. Chem.* **2008**, 18, 615–620.

160. Choi, S. J.; Oh, J. M.; Choy, J. H. Safety Aspect of Inorganic Layered Nanoparticles: Size-Dependency In Vitro and In Vivo. *J. Nanosci. Nanotechnol.* **2008**, 8, 5297–5301.

161. Ladewig, K.; Niebert, M.; Xu, Z. P.; Gray, P. P.; Lu, G. Q. Controlled Preparation of Layered Double Hydroxide Nanoparticles and their Application as Gene Delivery Vehicles. *Appl. Clay Sci.* **2010,** 48, 280–289.

162. Ladewig, K.; Niebert, M.; Xu, Z. P.; Gray, P. P.; Lu, G. Q. Efficient siRNA Delivery to Mammalian Cells using Layered Double Hydroxide Nanoparticles. *Biomaterials*, **2010**, 31, 1821–1829.

163. Li, A.; Qin, L.; Zhu, D.; Zhu, R.; Sun, J. Wang, S. Signalling Pathways Involved in the Activation of Dendritic Cells by Layered Double Hydroxide Nanoparticles. *Biomaterials*. **2010**, 31, 748–756.

164. Flesken-Nikitin, A.; Toshkov, I.; Naskar, J.; Tyner, K. M.; Williams, R. M.; Zipfel, W. R.; Giannelis, E. P.; Nikitn, A. Y. Toxicity and Biomedical Imaging of Layered Nanohybrids in the Mouse. *Toxicol Pathol*. **2007**, 35, 804–810.

165. Stahlmann, R. Safety Profile of the Quinolones. *J. Antimicrob. Chemoth*. **1990**, 26, 31–44.

166. Brighty, K. E.; Gootz, T. D. Chemistry and Mechanism of Action of the Quinolone Antibacterials. In *The Quinolones: Third Edition*; Andriole, V. T., Ed.; Academic Press: California, 2000; pp 33–97.

167. Davis, R.; Markham, A.; Balfour, J. A.; Ciprofloxacin. An Updated Review of Its Pharmacology, Therapeutic Efficacy and Tolerability. *Drugs*. **1996**, 51, 1019–74.

168. Stahlmann, R.; Lode, H. 2000. Safety Overview: Toxicity, Adverse Effects and Drug Interactions. In *The Quinolones: Third Edition*; Andriole, V. T.; Ed.; Academic Press: California, 2000; pp 397–453.

169. Kothur, K.; Singh, M.; Dayal, D. Ciprofloxacin-induced Anaphylactoid Reaction. *Eur. J. Pediatr*. **2006**, 165, 573–574.

170. Kelesidis, T.; Fleisher, J.; Tsiodras, S. Anaphylactoid Reaction Considered Ciprofloxacin Related: A Case Report and Literature Review. *Clin. Ther.* **2010**, 32, 515–526.

171. Caco, A. I.; Varanda, F.; de Melo, M. J. P.; Dias, A. M. A.; Dohrn, R.; Marrucho, I. M. Solubility of Antibiotics in Different Solvents. Part II. Non-Hydrochloride Forms of Tetracycline and Ciprofloxacin. *Ind. Eng. Chem. Res*. **2008**, 47, 8083–8089.

172. How, P.P.; Fischer, J. H.; Arruda, J. A.; Lau, A. H. Effects of Lanthanum Carbonate on the Absorption and Oral Bioavailability of Ciprofloxacin. *Clin. J. Am. Soc. Nephrol.* **2007**, 2, 1235–1240.

173. Frost, R. W.; Lasseter, K. C. ; Noe, A. J.; Shamblen, E. C.; Lettieri, J. T. Effects of Aluminum Hydroxide and Calcium Carbonate Antacids on the Bioavailability of Ciprofloxacin. *Antimicrob. Agents Ch.* **1992**, 36, 830–832.

174. Blanchemain, N., Karrout, Y.; N. Tabary, N.; M. Bria, M.; Neuta, C.; Hildebrand, H. F.; Siepmann, J.; Martel, B. Comparative Study of Vascular Prostheses Coated with Polycyclodextrins for Controlled Ciprofloxacin Release. *Carbohyd. Polym.* **2012**, 90, 1695–1703.

175. Jeong, Y. I.; Na, H. S.; Seo, D. H.; Kim, D. G.; Lee, H. C.; Jang, M. K.; Na, S. K.; Roh, S. H.; Kim, S. I.; Nah, J. W. Ciprofloxacin-encapsulated Poly(DL-Lactide-*co*-Glycolide) Nanoparticles and Its Antibacterial Activity. *Int. J. Pharm.* **2008**, 352, 317–323.

176. Park, S. N.; Kim, J. K.; Suh, H. Evaluation of Antibiotic-Loaded Collagen-Hyaluronic Acid Matrix as a Skin Substitute. *Biomaterials*. **2004**, 25, 3689–3698.

177. Somberg, J. C.; Molnar, J. The Pleiotropic Effects of Ethacrynic Acid. *Am. J. Ther.* **2009**, 16, 102–104.

178. Somberg, J. C.; Molnar, J. Therapeutic Approaches to the Treatment of Edema and Ascites: The Use of Diuretics. *Am. J. Ther*. **2009**, 98–101.

179. Kalish, R. S.; Wood, J. A.; Kydonieus, A.; Wille, J. J. Prevention of Contact Hypersensitivity to Topically Applied Drugs by Ethacrynic Acid: Potential Application to Transdermal Drug Delivery. *J. Control. Release*. **1997**, 48, 79–87.

180. Yamamoto, K.; Masubuchi, Y.; Narimatsu, S.; Kobayashi, S.; Horie, T. Toxicity of Ethacrynic Acid in Isolated Rat Hepatocytes. *Toxicology*. **2002**, 16, 151–158.

181. Allcock, H. R.; Pucher, S. R.; Angelo G, Scopelianos, A. G. Poly[(amino acid-ester)phosphazenes] as Substrates for the Controlled Release of Small Molecules. *Biomaterials,* **1994**, 15, 563–569.

182. Schärtl, W. *Light Scattering from Polymer Solutions and Nanoparticle Dispersions*; Springer-Verlag: Heidelberg, 2007; pp 16–18.

183. Nahler, G. *Dictionary of Pharmaceutical Medicine*: *Third Edition*; Springer-Verlag: Heidelberg, 2013; pp 135–136.

184. Gu, Z.; Thomas, A. C.; Xu, Z. P.; Campbell, J. H.; Lu, G. Q. In Vitro Sustained Release of LMWH from MgAl-Layered Double Hydroxide Nanohybrids. *Chem. Mater*. **2008**, 20, 3715–3722.

185. Mosmann, T. Rapid Colorimetric Assay for Cellular Growth and Survival: Application to Proliferation and Cytotoxicity Assays. *J. lmmunol. Methods*. **1983**, 65, 55–63.

186. Kovar, P.; Pospisil, M.;Kafunkova, E.; Lang, K.; Kovanda, F. Mg-Al Layered Double Hydroxide Intercalated with Porphyrin Anions: Molecular Simulations and Experiments. *J. Mol. Model*. **2010**, 16, 223–233.

187. Miyata, S. Anion-Exchange Properties of Hydrotalcite-like Compounds. *Clays Clay Miner*. **1983**, 31, 305-311.

188. Wu, G.; Wang, L.; Yang, L.; Yang, J. Factors Affecting the Interlayer Arrangement of Transition Metal–Ethylenediaminetetraacetate Complexes Intercalated in Mg/Al Layered Double Hydroxides. *Eur. J. Inorg. Chem*. **2007**, No.6, 799–808.

189. Duan, X.; Lu, J.; Evans, D. G. 2011. Assembly Chemistry of Anion-Intercalated Layered Materials. In *Modern Inorganic Chemistry*; Xu, R, Pang, W, Huo, Q., Eds.; Elsevier: Amsterdam, 2011; pp 375–404.

190. Marangoni, R.; Ramos, L. P.; Wypych. F. New Multifunctional Materials Obtained by the Intercalation of Anionic Dyes into Layered Zinc Hydroxide Nitrate Followed by Dispersion into Poly(Vinyl Alcohol) (PVA). *J. Colloid Interf. Sci*. **2009**, 330, 303–309.

191. Taibi, M.; Ammar, S.; Jouini, N.; Fievet, F.; Molinie, P.; Drillon, M. Layered Nickel Hydroxide Salts: Synthesis, Characterization and Magnetic Behaviour in Relation to the Basal Spacing. *J. Mater. Chem*. **200**2, 12, 3238–3244.

192. Kafunkova, E.; Taviot-Gueho, C.; Bezdicka, P.; Klementov, M.; Kovar, P.;Kubat, P .;Mosinger, J.; Pospisil, M.; Lang, K. Porphyrins Intercalated in Zn/Al and Mg/Al Layered Double Hydroxides: Properties and Structural Arrangement. *Chem. Mater*. **2010**, 22, 2481–2490.

193. Stahlin, W.; Oswald, H. R. *Acta Crystallogr. Sect. B*. **1970**, 26, 860.

194. Kovanda, F.; Maryskova, Z.; Kovar, P. Intercalation of Paracetamol into the Hydrotalcite-like Host. *J. Solid State Chem*. **2011**, 184, 3329–3335.

195. Iyi, N.; Kurashima, K.; Fujita, T. Orientation of an Organic Anion and Second-Staging Structure in Layered Double-Hydroxide Intercalates. *Chem. Mater*. **2002**, 14, 583–589.

196. Kumar, P.; Kalinichev, A.G.; Kirkpatrick, R. J. Hydration, Swelling, Interlayer Structure, and Hydrogen Bonding in Organolayered Double Hydroxides: Insights from Molecular Dynamics Simulation of Citrate-Intercalated Hydrotalcite. *J. Phys. Chem. B*. **2006**, 110, 3841–3844.

197. Preparation and Photo-Physical Characterisation of Nanocomposites Obtained by Intercalation and Co-intercalation of Organic Chromophores into Hydrotalcite-like Compounds. Aloisi, G. G.; Costantino, U.; Elisei, F.; Latterini, L.; Natali, C.; Nocchetti, M. *J. Mater. Chem*. **2002**, 12, 3316–3323.

198. Ogawa, M.; Asai, S. Hydrothermal Synthesis of Layered Double Hydroxide-Deoxycholate Intercalation Compounds. *Chem. Mater*. **2000**, 12, 3253–3255.

199. Tronto, J.; Crepaldi, E. L.; Pavan, P. C., De Paula, C. C.; Valim, J. B. Organic Anions of Pharmaceutical Interest Intercalated in Magnesium Aluminum LDHs by Two Different Methods. *Mol. Crysl. Liq. Cryst*. **2001**, 356, 227-237.

200. Anderson, R. L.; Christopher Greenwell, H.; Suter, J. L.; Coveney, P. V.; Thyveetil, M. A. Determining Materials Properties of Natural Composites using Molecular Simulation. *J. Mater. Chem*. **2009**, 19, 7251–7262.

201. Reichenbacher, M.; Popp, J. Vibrational Spectroscopy. *Challenges in Molecular Structure Determination;* Springer: Berlin, 2012; pp 63–143.

202. Theokloprogge, J.; Wharton, D.; Hickey, L.; Frost, R. L. Infrared and Raman Study of Interlayer Anions CO_3^{2-}, NO_3^-, SO_4^{2-} and ClO_4^- in Mg/Al Hydrotalcite. *Am. Mineral.* **2002**, 87, 623–629.

203. Vieira, A. C.; Moreira, R. L.; Dias, A. Raman Scattering and Fourier Transform Infrared Spectroscopy of $Me_6Al_2(OH)_{16}Cl_2{\cdot}4H_2O$ (Me = Mg, Ni, Zn, Co, and Mn) and $Ca_2Al(OH)_6Cl{\cdot}2H_2O$ Hydrotalcites. *J. Phys. Chem. C.* **2009**, 113, 13358–13368.

204. Benito, P.; Labajos, F. M.; Rives, V. Uniform Fast Growth of Hydrotalcite-like Compounds. *Cryst. Growth Des.* **2006**, 6, 1961–1966.

205. Hibino, T.; Yamashita, Y.; Kosuge, K.; Tsunashima, A. Decarbonation Behavior of Mg-Al-CO_3 Hydrotalcite-like Compounds During Heat Treatment. *Clays Clay Miner.* **1995**, 43, 427-432.

206. Ruiz, P.; Ortiz, R.; Perello, L.; Alzuet, G.; Gonzalez-Alvarez, M.; Liu-Gonzalez, M.; Sanz-Ruiz, F. Synthesis, Structure, and Nuclease Properties of Several Binary and Ternary Complexes of Copper(II) with Norfloxacin and 1,10 Phenantroline. *J. Inorg. Biochem.* **2007**, 101, 831–840.

207. Hernandez-Gil, J.; Perello, L.; Ortiz, R.; Alzuet, G.; Gonzalez-Alvarez, M.; Liu-Gonzalez, M. Synthesis, Structure and Biological Properties of Several Binary and Ternary Complexes of Copper(II) with Ciprofloxacin and 1,10 Phenanthroline. *Polyhedron.* **2009**, 28, 138–144.

208. Khan, A. I.; Williams, G. R.; Hu, G.; Rees, N. H.; O'Hare, D. The Intercalation of Bicyclic and Tricyclic Carboxylates into Layered Double Hydroxides. *J. Solid State Chem.* **2010**, 183, 2877–2885.

209. Deacon, G. B.; Phillips, R. J. Relationships between the Carbon-Oxygen Stretching Frequencies of Carboxylato Complexes and the Type of Carboxylate Coordination. *Coord. Chem. Rev.* **1980**, 33, 227-250.

210. Wu, G.; Wang, L.; Evans, D. G.; Duan, X. Layered Double Hydroxides Containing Intercalated Zinc Sulfide Nanoparticles: Synthesis and Characterization. *Eur. J. Inorg. Chem*. **2006**, No. 16, 3185–3196.

211. Lutz, H. D.; Haeuseler, H. Infrared and Raman Spectroscopy in Inorganic Solids Research. *J. Molec. Str*. **1999**, 511–512, 69–75.

212. Turel, I. The Interactions of Metal Ions with Quinolone Antibacterial Agents. *Coordination Chemistry Reviews*. **2002**, 232, 27–47.

213. Turel, I.; Bukovec, P. Comparison of the Thermal Stability of Ciprofloxacin and Its Compounds. *Thermochim. Acta*. **1996**, 287, 311–318.

214. Roelofs, J.C.A.A.; van Bokhoven, J.A.; van Dillen, A.J.; Geus, J.W.; de Jong, K.P. The Thermal Decomposition of Mg–Al Hydrotalcites: Effects of Interlayer Anions and Characteristics of the Final Structure. *Chem. Eur. J*. **2002**, 8, 5571–5579.

215. Rives, V. Characterisation of Layered Double Hydroxides and Their Decomposition Products. *Mater. Chem. Phys*. **2002**, 75, 19–25.

216. Malherbe, F.; Besse, J.P. Investigating the Effects of Guest-Host Interactions on the Properties of Anion-Exchanged Mg–Al Hydrotalcites. *J. Solid State Chem*. **2000**, 155, 332–341.

217. Zhang, H.; Zou, K.; Guo, S.; Duan. X. Nanostructural Drug-Inorganic Clay Composites: Structure, Thermal Property and In Vitro Release of Captopril-Intercalated Mg–Al-Layered Double Hydroxides. J. Solid State Chem. 2006, 179, 1792–1801.

218. Malherbe, F.; Forano, C.; Besse, J. P. Use of Organic Media to Modify the Surface and Porosity Properties of Hydrotalcite-like Compounds. *Micropor. Mater*. **1997**, 10, 67–84.

219. Saiah, F. B. D.; Su, B. L.; Bettahar, N. Removal of Evans Blue by using Nickel-Iron Layered Double Hydroxide (LDH) Nanoparticles: Effect of Hydrothermal Treatment Temperature on Textural Properties and Dye Adsorption. *Macromol. Symp*. **2008**, 273, 125–134.

220. Zhang, H.; Pan, D.; Zou, K.; He, J.; Duan, X. A Novel Core-Shell Structured Magnetic Organic-Inorganic Nanohybrid Involving Drug-Intercalated Layered Double Hydroxides Coated on a Magnesium Ferrite Core for Magnetically Controlled Drug Release. *J. Mater. Chem.* **2009**, 19, 3069–3077.

221. Qi, L.; Xu, Z.; Jiang, X.; Hu, C.; Zou, X. Preparation and Antibacterial Activity of Chitosan Nanoparticles. *Carbohydr. Res.* **2004**, 339, 2693–2700.

224. Anthony R. Auxilio, A. R.; Philip C. Andrews, P. C.; Peter C. Junk, P. C.; Leone Spiccia, L.; Daniel Neumann, D.; Warwick Raverty, W.; Vanderhoek, N. Adsorption and Intercalation of Acid Blue 9 on Mg–Al Layered Double Hydroxides of Variable Metal Composition. *Polyhedron.* **2007**, 26, 3479–3490.

225. Rojas, R.; Ulibarri, M. A.; Cristobalina Barriga, C.; Rives, V. Intercalation of Metal-Edta Complexes in Ni–Zn Layered Hydroxysalts and Study of Their Thermal Stability. *Micropor. Mesopor. Mater.* 2008, 112, 262–272.

226. Merkus, H. G. *Particle Size Measurements. Fundamentals, Practice, Quality;* 2009; Springer: Berlin. pp 299–317.

227. Woehrle, G. H.; Hutchison, J. E.; Ozkar, S.; Finke, R. G. Analysis of Nanoparticle Transmission Electron Microscopy Data Using a Public-Domain Image-Processing Program, Image. *Turk. J. Chem.* **2006**, 30, 1–13.

228. Fillafer, C.; Wirth, M.; Gabor. F. Stabilizer-Induced Viscosity Alteration Biases Nanoparticle Sizing via Dynamic Light Scattering. *Langmuir.* **2007**, 23, 8699–8702.

229. Klang, V.; Valenta, C.; Matsko, N. B. Electron Microscopy of Pharmaceutical Systems. *Micron*, **2013**, 44, 45–74.

230. *DLS Technical Notes. Dynamic Light Scattering: An Introduction in 30 Minutes;* Malvern Instruments Ltd: Worchestershire UK.

231. Low, M.J.D. Kinetics of Chemisorption of Gases on Solids. *Chem. Rev.* **1960**, 60, 267–312.

232. Ribeiro, C.; Arizaga, G.G.C.; Wypych, F.; Sierakowski, M. R. Nanocomposites Coated With Xyloglucan For Drug Delivery: In Vitro Studies. *Int. J. Pharm.* **2009**, 367, 204–210.

233. Varum, F.J.O.; Hatton, G.B.; Basit, A.W. Food, Physiology and Drug Delivery. *Int. J. Pharm.* **2013**.

234. Li, B.; He, J.; Evans, D. G.; Duan, X. Enteric-Coated Layered Double Hydroxides as a Controlled Release Drug Delivery System. *Int. J. Pharm.* **2004**, 287, 89–95.

235. Wong, Y.; Markham, K.; Xu, Z. P.; Chen, M.; Lu, G. Q.; Bartlett, P. F.; Cooper, H. M. Efficient Delivery of siRNA to Cortical Neurons using Layered Double Hydroxide Nanoparticles. *Biomaterials*. **2010**, 31, 8770–8779.

236. Gu, Z.; Rolfe, B. E.; Xu, Z. P.; Thomas, A. C.; Campbell, J. H.; Lu, G. Q. Enhanced Effects of Low Molecular Weight Heparin Intercalated with Layered Double Hydroxide Nanoparticles on Rat Vascular Smooth Muscle Cells. *Biomaterials*. **2010**, 31, 5455–5462.

237. Molnar, J.; Somberg, J. C. The Clinical Pharmacology of Ethacrynic Acid. *Am. J. Ther.* **2009**, 16, 102–104.