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Review article

Layered double hydroxide nanoparticles for biomedical applications: Current status and recent prospects

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ABSTRACT

Layered double hydroxides (LDH), also known as hydrotalcite like compounds are well known for their peculiar characteristics like good biocompatibility, anion exchange capacity, high chemical stability and pH-dependent solubility which aid for the design of smart drug delivery systems. This review focuses on the most recent progress in the synthesis of LDH along with the current methods for controlling the structural properties and chemical functionalization for biotechnological and biomedical applications. The recent research on the pathways of particle entry into the cells is described. One of the promising areas of interest in nanotechnology is the development of targeted drug delivery systems with controlled release properties; the contribution of LDH towards these topics is also summarized. In addition, we highlighted the significant achievements made in the delivery of genes and imageable agents using LDH. Further we briefly conferred the latest breakthroughs in the fabrication of hybrid LDH for obtaining novel properties followed by the applications of LDH in various fields of biomedicine. We critically discuss burning questions especially related to the toxicological evaluation of LDH nanoparticles in order to enable a fast transition to clinical trials of this promising drug delivery platform.

1. Introduction and scope for controlled synthesis and functionalization

The most fascinating aspect in the advent of nanotechnology is the invention of layered double hydroxide (LDH) nanomaterials that might rule the pharmaceutical industry globally in the near future. Materials with a particle size ranging from 1 to 100 nm in one or more external dimensions are commonly termed as nanomaterials/nanostructures and the branch of science that deals with the design and manufacture of these tiny particles is known as nanotechnology. Nanotechnology is without a doubt the most successful mankind's inventions. This technology is currently of immense interest with not only arising new applications but also adding flexibility to existing systems in various fields of science as diverse as agriculture (Gonzalez-Melendi et al., 2008), medicine (Xia, 2008), electronics (Subramanian and Lee, 2012), biomaterials (Katz et al., 2005), energy production (Chen et al., 2012b) and storage (Arico et al., 2005). The integration of nanotechnology with life science is one such exciting new direction that have opened a door to a wide range of biomedical applications improving many of the current challenges in fields such as disease diagnosis and therapy. Many polymer based nano drug delivery systems have entered clinics (Reimer and Balzer, 2003; Rivera Gil et al., 2010) and an even greater number are currently in preclinical stages of development (Davis et al., 2008; Bu et al., 2012; Rosenholm et al., 2012). Among the inorganic nanomaterials studied, LDHs are considered as the most biocompatible nanoconstructs (Liang et al., 2014) and have received considerable attention in recent years. Since their discovery in 1842 by Swedish scientists, there has been considerable scientific research on the controlled synthesis and applications of LDH and their progress in various fields of biomedicine has been summarized in few reviews (Xu and Lu, 2006; Choy et al., 2007; Del Hoyo, 2007; Choi and Choy, 2011; Khot et al., 2012). Some interesting advances have emerged ever since the reviews published by Ladewig (Ladewig et al., 2009) and Rives (Rives et al., 2014) on the application of LDH in selected fields of biomedicine. These precise reviews gave a summary of selected recent developments in this exciting, ever expanding field. Inspired by these reviews, herewith we have compiled the recent developments made in the field which are categorized into following sections named particle uptake mechanisms, controlled and sustained drug release properties, delivery of bioactive moieties, hybrid nanoconstructs, imaging and targeting.

2. Particle uptake mechanisms

Mechanism of cellular uptake using nanoparticles can be regarded as one of the crucial factors that could determine the rate of cytotoxicity in biological environment which facilitates a greater control in predicting the cytotoxic effects. Very few groups have investigated the role of charge, mechanism of uptake and intracellular localization of LDH. The first ever to report that neutrally charged or positively charged LDH nanoconstructs that are highly efficient in trapping anionic molecules

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facilitating an ease of attachment with the negatively charged cell membranes (Choy et al., 2000, 2004a) and also stated that LDHs are taken up by cells via clathrin-mediated endocytosis (Oh et al., 2006a, 2009; Choi and Choy, 2011).

In another study Oh et al. (2009) has evaluated the role of LDH particle size in cellular uptake. They synthesized four kinds of hexagonal LDH nanoparticles with various sizes and studied the uptake in osteosarcoma cells. The results showed size dependent uptake of particles in the order of 50 > 200 > or = 100 > 350 nm, which suggest that particles smaller in size are more efficient in penetrating the cellular membranes than the large state counter parts. Another interesting finding in this study is that only particles that ranged within a size of 200 nm are uptaken by the cells via clathrin-mediated endocytosis whereas in contrast the larger counter parts entered the cells without any specific cellular entry pathway providing a new perspective to design LDH for biological purposes. It was further demonstrated that particles with all dimensions were up taken by the cells within a time span of 15 min irrespective of their size. Interestingly, 50 nm particles showed a high uptake efficacy in the initial stages (up to 8 h) whereas the particles with higher dimensions reached a flattened state after 2 h of incubation. It is interesting to find that intracellular concentration of all the particles increased in a concentration dependent manner suggesting a possible scope for receptor mediated endocytotic uptake (Oh et al., 2009). The particle retention studies showed that particles with larger dimensions (100-350 nm) tend to have longer retention time than the particles with smaller dimensions suggesting a possible scope to design drug intercalated LDH according to the required level of retention time (Oh et al., 2009).

Li et al. (2013b) studied the morphological effects on the particle uptake mechanism. Particles with two different sizes; 20 nm $[Mg_3Al(OH)_8](CO_3)_{0.5}$; ($CO_3$-LDH) and 180 nm $[Mg_3Al(OH)_8]NO_3$; (NO_3-LDH) were synthesized and further conjugated with fluorescein isothiocyanate (FITC) to the particle surface to study the uptake in Mouse Motor Neuron (NSC 34) cells. The results disclosed a similar kind of uptake as reported by Chung et al. (2012) for particles within 100 nm range where the particle uptake increased with concentration. In this interesting study, it is important to note that the particle with 20 nm size localized in the nucleus of cells whereas the large sized particles with 180 nm remained in the cytoplasm (Li et al., 2013b) (Fig. 1). These attractive findings have altogether revolutionized the field of drug delivery and diagnosis. For instance, recent report suggested that methotrexate conjugated LDH were more efficient in penetrating the cellular membranes maintaining high intracellular drug concentrations than the free drugs which is attributed to the clathrin mediated endocytotic uptake of LDH-drug conjugates and further it is found that drug conjugated LDH are more efficient against human osteosarcoma (SaOS-2) cancerous cell lines than the free drugs (Choi et al., 2012).

In other research findings the evaluation was performed for the efficacy of methotrexate intercalated LDH in overcoming multi-drug resistance in methotrexate resistant cancer cell lines. The results showed

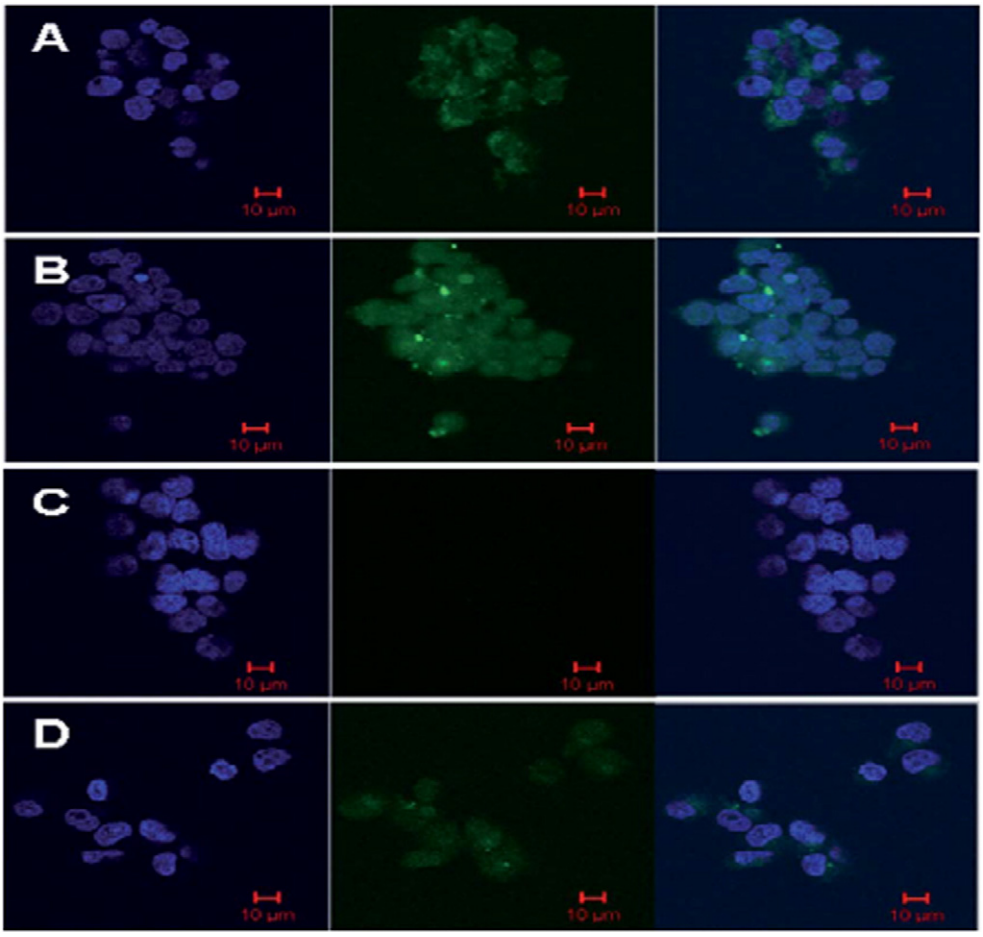

Fig. 1. Confocal microscopic images of intracellular localization in NSC 34 cells: (A) 6.25 µg/ml of CO_3LDH-FITC incubated for 2.5 h; (B) 10 µg/ml of CO_3LDH-FITC, incubated for 3 h; (C) control experiment performed with supernatant solution using 17 µg/ml of CO_3-LDH-FITC, incubated for 3 h and (D) free 6.25 µg/ml FITC anions alone incubated for 4 h. Reprinted from Journal of Material Chemistry B. Vol. 1. Shuangde Li, Jinghuan Li, Chengle J. Wang, Qiang Wang, M. Zameel Cader, Jun Lu, David G. Evans, Xue Duan, Dermot O'Hare, Cellular uptake and gene delivery using layered double hydroxide nanoparticles, pp. 61-68. Copyright (2012), with permission from Royal Society of Chemistry.