Biological Properties of Nanoiron

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Abstract — **Iron oxide nanoparticles have been widely used experimentally for numerous applications such as magnetic resonance imaging contrast enhancement, tissue repair, immunoassay, detoxification of biological fluids, hyperthermia, drug delivery, cell separation, treatment of iron deficiency anemia etc.Due to their extraordinary reduction capabilities, small size in the range of several tens of nanometers and high reactivity with a broad spectrum of toxic substances, these ultrafine particles are highly applicable in the reduction technologies of ground water remediation and waste water treatment. Nanoiron has attracted a great deal of attention in nanomedicine over the past decade. Ferumoxytol is a novel intravenous nanoiron product that can be administered in treatment of iron deficiency anemia. Iron oxide nanoparticles have proven to be highly effective contrast agents for the magnetic resonance imaging diagnosis of a variety of diseases and pathologic processes.**

Index Terms — **iron, nanoiron, nanoparticles, treatment.**

I.INTRODUCTION

Nanoparticles have attracted considerable attention for their novel physical and chemical properties. Nanotechnology will contribute to the creation and the development of products with improved mechanical, chemical, biological, optical, electronic properties and of drugs with distinct therapeutic effect [1, 3].

Currently the properties of nanometals are studied actively [2, 5]. Iron (Fe) is one of the most abundant rock-forming elements, constituting about 5% of the Earth's crust. It is the fourth most abundant element after oxygen, silicon and aluminium, and after aluminium, the most abundant and widely distributed metal. The unique properties of nanoparticles, their ability to participate in biodegradation and biotransformation, relative prevalence and low cost of this metal contributed to initation of several studies with nanoparticles of iron and iron oxide [4, 7].

Iron oxide nanoparticles have been widely used experimentally for numerous in vivo applications such as magnetic resonance imaging contrast enhancement, tissue repair, immunoassay, detoxification of biological fluids, hyperthermia, drug delivery, cell separation, treatment of iron deficiency anemia etc. [6, 7].

The main task of our study was to analyze the known of biological properties of nanoiron.

II. RESULTS AND DISCUSSION

In last years, scientists in the world pay attention to studying the pharmacological properties of nanoiron. It is known that microscopic particles of iron oxidize easily. If iron oxidation is produced in the presence of xenobiotics of organic origin (trichlorethylene, dioxin, carbon tetrachloride etc.) these complexes of molecules are broken down into simpler and much less toxic structures. Similar phenomena are observed at iron oxidation in the presence of heavy metals (mercury, lead, nickel, zinc, uranium). In this case insoluble complexes stored in the soil are obtained, which do not penetrate the plant composition, and therefore the food. Thus, the negative impact of organic and inorganic xenobiotics on environment is significantly reduced [10]. Nanoiron is 10-1000 times more active than conventional macroscopic particles of iron, so his detoxifying effect is much more significant. This is due to the easily penetration of iron nanoparticles into the polluted environment, and they are well tolerated by groundwater in environmental cleansing process. The biological property of nanoiron is not influenced by pronounced acidity, temperature and the presence of other substances in soil [8, 10].

Reactions involving iron play a major role in the environmental cycling of a wide range of important organic, inorganic and radioactive contaminants. Due to their extraordinary reduction capabilities, small size in the range of several tens of nanometers and high reactivity with a broad spectrum of toxic substances, these ultrafine particles are highly applicable in the reduction technologies of ground water remediation and waste water treatment. In comparison with other frequently used procedures for water treatment, the treatment exploiting of Fe(0) nanoparticles represents environmentally friendly technology since non-toxic and nature-abundant iron oxides (mainly magnetite - Fe_3O_4) are the products of transformation of Fe (0) [8, 11].

In-situ application consists in injection of nanoparticles through small boreholes directly into the contaminated groundwater. Zero-valent iron nanoparticles (nZVI) injection is very fast, reaching significantly lower operating costs compared to commonly used remediation methods (expensive construction of reactive barriers, building of pump&treat stations, excavation of contaminated soil etc.). In comparison to other in-situ technologies a far lower quantities of nZVImaterial is needed due to high efficiency of the product and thus the time (and subsequently the price) further reduces costs of remediation project [7, 8].

Pentachlorophenol (PCP) was extensively used in the past for the preservation of wood and wood products, and its release into the environment caused extensive contamination of subsurface soils [10]. Thus, was examinated the enhanced delivery of zero valentnanoiron particles amended with surfactant or cosolvent under electric field for the remediation of a low permeable kaolin soil spiked with pentachlorophenol (1000 mg/kg of dry soil). Bench-scale electrokinetic experiment was conducted first using bare nanoiron suspension (50-300 nm particle size; 5 g/L concentration) in anode and applying an electric potential of 1 VDC/cm. Results revealed that only limited amount of nanoiron could be transported into the soil due to aggregation and settlement as well as partial oxidation of nanoiron within the anode. Additional experiments were conducted using nanoiron amended with a nonionic surfactant (5% Igepal CA720) or a cosolvent (5% ethanol) in anode and applying the same electric potential of 1 VDC/cm. Results showed that the electroosmotic flow was not influenced significantly by the amendment; however, the transport of nanoiron was limited similar to the experiment with bare nanoiron. PCP was partially degraded in all of the experiments not because of nanoiron, but mainly due to reductive dechlorination at cathode. The extent of PCP reduction was slightly more in the cosolvent system, possibly due to enhanced solubilization and transport of PCP into cathode. Overall, it is shown that new strategies are needed to prevent aggregation, settlement and oxidation of nanoiron for effective electrokinetic delivery of nanoiron and remediation of PCP in low permeability soils [8, 9].

Research conducted by Nanobakt Ltd. has led to the development of an iron colloid product containing iron/iron-hydroxide nanoparticles. Due to the reductive properties of ZVI nanoparticles, this dispersion is effective in eliminating toxic organic compounds in soil. When nano iron particles in the product come in contact with polluted soil, they act to reduce halogenated pollutants.

$$2Fe^0 + 3H_2O + XCl \rightarrow 2Fe^{2+} + 3OH^- + H_2 + X\text{-}H + Cl^-$$

The product contains iron particles with a diameter of a few nanometres. An electron microscope image and compound analysis are shown in fig. 1.

Zero-valent iron has been shown to be a strong reducing agent capable of reducing many halogenated methanes, ethanes, and ethenes and other halogenated compounds at ambient temperatures. A permeable reactive barrier (PRB) is an engineered zone of reactive material, extending below the water table, designed to intercept and treat contaminated groundwater.

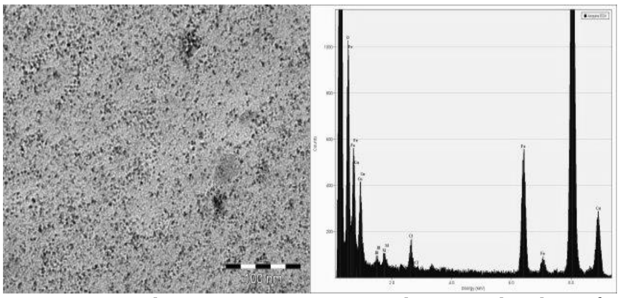

Fig.1. Electron microscope image and compound analysis of nanoiron particles.

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Zero-valent iron-based permeable reactive barriers are one of the more established so-called “novel” iron-based treatment tools, however predicting the long-term performance of these systems remains problematic due to their complex chemistry. There has been much recent interest in the use of engineered iron-based nanoparticles as an in-situ, relatively non-invasive tool for groundwater remediation, particularly for the direct treatment of contaminant source zones, but uncertainties over the health impacts and environmental fate of these particles need to be addressed before their widespread application.

Nanoiron has attracted a great deal of attention in nanomedicine over the past decade.

Iron deficiency is an important cause of anemia in patients with chronic kidney disease (CKD), but intravenous iron is infrequently used among patients who are not on dialysis. Ferumoxytol is a novel intravenous iron product that can be administered as a rapid injection. Ferumoxytol has a colloidal particle size of 30 nm and a molecular weight of 750 kD. Ferumoxytol injection is a sterile liquid with a neutral pH, formulated with mannitol for isotonicity; each milliliter contains 30 mg of iron and 44 mg of mannitol. Among patients who were not receiving erythropoiesis-stimulating agents, hemoglobin increased 0.62 ± 1.02 g/dl with ferumoxytol and 0.13 ± 0.93 g/dl with oral iron. Among patients who were receiving erythropoiesis-stimulating agents, hemoglobin increased 1.16 ± 1.49 g/dl with ferumoxytol and 0.19 ± 1.14 g/dl with oral iron. Treatment-related adverse events occurred in 10.6% of patients who were treated with ferumoxytol and 24.0% of those who were treated with oral iron; none was serious. In summary, a regimen of two doses of 510 mg of intravenous ferumoxytol administered rapidly within 5 ± 3 d was well tolerated and had the intended therapeutic effect. This regimen may offer a new, efficient option to treat iron deficiency anemia in patients with CKD [12] .

Due to advances in nanotechnology, exposure to particle compounds in the workplace has become unavoidable. Assessment of their toxicity on health is an important occupational safety issue. This study was conducted in mice to investigate the toxicological effects of submicron and nano-iron oxide particles on pulmonary immune defences. In that purpose, we explored for the first time, inflammatory and immune responses in lung-associated lymph nodes. For each particle type, mice received either a single intratracheal instillation at different concentrations (250, 375, or 500µg/mouse) or four repeated instillations at 500µg/mouse each. Cytokine production, inflammatory and innate immune response, and humoral immune response were respectively assessed 1, 2, and 6 days after particle exposures. Both types of particles induced lung inflammation associated with increased cytokine productions in lymph node cell cultures and decreased pulmonary immune responses against sheep erythrocytes. Natural killer activity was not modified by particles. In comparison to single instillation, repeated instillations resulted in a reduction of inflammatory cell numbers in both bronchoalveolar lavages and pulmonary parenchyma. Moreover, the single instillation model demonstrated that, for a same dose, nano-iron oxide particles produced higher levels of inflammation and immunodepression than their submicron-sized counterparts [13].

In the immediate future, the reviewers see that perhaps the most likely application of iron oxide nanoparticles (IONPs) will be as an magnetic resonance imaging (MRI) contrast agent. This is because IONPs offer several important advantages over commonly available gadolinium based contrast agents; including, but not limited to, lower toxicity. They can be used to diagnose a variety of pathologies and biological activities such as inflammation, infarction and tissue repair. In addition to improved diagnostic outcomes, there can also be tailored therapeutic functions, in particular with tumour treatment. IONPs can be binded with antibodies, drugs, enzymes and proteins. They can be directed to specific organs or tissues and can also be guided with magnetic fields to target tumours and induce hyperthermic effects. Multifunctional iron oxide nanoparticles, together with MRI, offer unique advantages with diagnostic and therapeutic capabilities. In particular, molecular imaging with IONPs and MRI has the potential to heavily impact upon early detection of a variety of diseases and pathologic processes. It can also be used to devise treatment approaches dedicated to individual patient circumstances. This should all lead to improved patient outcomes. These are areas of high research activity and there is no doubt that this will lead to a new frontier in magnetic resonanceimaging [1, 5].

Thus, it is important to continue the investigations of iron nanoparticles pharmacological effects on living organisms and to create methods for detection of nanoparticles in the environment.

III. CONCLUSIONS

Thus, iron nanoparticles produce the following novel properties:

1. Reactions involving iron nanoparticles play a major role in the environmental cycling of a wide range of important organic, inorganic and radioactive contaminants.
2. Parenteral iron formulations containing iron nanoparticles such us Ferumoxytol are among the products currently used for the treatment of iron deficiency anemia.
3. The most likely application of iron oxide nanoparticles will be as an magnetic resonance imaging (MRI) contrast agent to diagnose a variety of pathologies and biological activities such as inflammation, infarction, cancer and tissue repair.

REFERENCES

[1]. J. H. Thrall. Nanotechnologyandmedicine. *Radiology*, vol. 230, no. 2, pp. 315-318, 2004.

[2]. Б. Патон, В.Москаленко, І.Чекман, Б. Мовчан. Нанонаука і нанотехнології: технічний, медичний та соціальний аспекти, *Вісн. НАН України*, № 6., с. 18-26, 2009.

[3]. І. С. Чекман.Нанонаука: перспективи наукових досліджень. *Наука та інновації*, т. 5, №3, с. 89-93, 2009.

[4]. A. El-Ansary, S. Al-Dalhan. ”On the toxicity of therapeutically used nanoparticles: an overview”. *J. Toxicol*., pp. 1-9, 2009.

[5]. V. Cabuil. Magnetic nanoparticles. *Dekker encyclopedia of nanoscience and nanotechnology, CRC Press, Taylor and Francis Group, Boca Raton*, FL., vol. 3, pp. 1985–2000, 2008.

[6]. D. L. Huber. Iron nanoparticles. *Dekker encyclopedia of nanoscience and nanotechnology, CRC Press, Taylor and Francis Group, Boca Raton*, FL., vol. 3, pp. 1681–1687, 2008.

[7]. S. Laurent, D. Forge, M. Port et al. ”Magnetic iron oxide nanoparticles: synthesis, stabilization, vectorization, physicochemical characterizations, and biological applications”. *Chem. Rev*., vol. 108, no. 6, pp. 2064–2110, 2008

[8]. I. M. Lo, R.Y. Surampalli, K.C. Lai. ”Zero-valent iron reactive materials for hazardous waste and inorganics removal”. *Reston, Virginia: American Society of Civil Engineers (ASCE)*, pp. 343, 2007.

[9]. R.D. Ludwig, C. Su, T. R. Lee. ”In situ chemical reduction of Cr(VI) in groundwater using a combination of ferrous sulphate and sodium dithionite: a field investigation”. *Environ Sci Technol*, no. 41, pp. 5299–305, 2007.

[10]. B. Nowack, T. Bucheli. ”Occurrence, behavior and effects of nanoparticles in the environment”. *Environ Pollut.*, no. 150, pp.5–22, 2007.

[11]. Deng B, Hu S. ”Reductive dechlorination of chlorinated solvents on zerovalent iron surfaces”. *In: Smith JA, Burns SE, editors. Physicochemical groundwater remediation,* New York: Kluwer Academic; pp. 139–59, 2001.

[12]. D.S. Spinowitz, A.T. Kausz, S.D. ”Nobleetal. Ferumoxytolfortreatingirondeficiencyanemia in CKD”. *J. Am. Soc. Nephrol*, vol. 19, pp. 1599-1605, 2008.

[13]. M. Ban, I. Langonné, N. Huguet, M. Goutet. Effect of submicron and nano-iron oxide particles on pulmonary immunity in mice. Toxicol Lett, vol. 210, no. 3, pp. 267-75, Feb 2012.