Multifunctional Drug Nanosystems: A Summary of Recent Researches at IMS/VAST

X.P. Nguyen[1], T.T.TMai[1], P.T. Ha[1], H.N. Pham[1], H.N. Luu[1], H.M. Do[1], D.L. Tran[1], H.N. Nguyen[1], L.T. Nguyen[2], A.S. Ho[2], and T.M.N. Hoang[3]

[1] Lab. of Biomedical Nanomaterials, Institute of Materials Science (IMS/VAST), 18 Hoang Q. Viet, Hanoi, Vietnam
[2] Academy of Military Medicine, Ha Dong, Hanoi, Vietnam
[3] University of Natural Sciences, Vietnam National University, 334 Nguyen Trai, Hanoi, Vietnam

Abstract— **The main task of nanomedicine is to fabricate, normally by chemical engineering, nanoscale systems that can play various functions of both diagnosis and treatment. This report aims to present some researches, carried out by the Laboratory of Biomedical Nanomaterials (IMS/VAST in Hanoi), on fabrication and characterization of nanovectors for the disease of cancer. The first part deals with magnetite (Fe_3O_4) nanoparticles (MNPs) based nanoconjugates, functionalized by coating with several polymers as well as loaded with a drug of curcumin. The used MNPs were obtained by co-precipitation, exhibited spherical shape of diameter of 15-20 nm, saturation magnetization of M_s ~ 65-70 emu/g. The coating polymers were acrylic acid (PAA), chitosan (CS) and Alginate (Alg) which were confirmed using the infrared (FTIR) spectra. Magnetic Inductive Heating (MIH) measurements demonstrated that the fabricated MNPs-based conjugates exhibited quite high heating performance, perspective for hyperthermia application. The application of Fe_3O_4@PAA for *in-vivo* hyperthermia treatment of cancer incubated on mice will be shown. As for imaging application, the Fe_3O_4@CS@Cur was used to demonstrate a dual possibilities, fluorescence and magnetic resonance, of monitoring cell penetration by macrophage. In the second part, we show a recent study on targeted delivery systems of paclitaxel/doxorubicin/curcumin-loaded copolymer/polymer nanoparticles, which were prepared by a modified solvent extraction/evaporation technique and decorated by folic acid. The obtained spherical nanoparticles were negatively charged with a zeta potential of about – 30 mV with the size around 50 nm and a narrow size distribution. The targeting effect of anticancer-drugs nanoparticles with folate decoration was investigated *in vitro* by the uptake in cancer cell lines and in nude mouse. The results indicate that the targeted paclitaxel/doxorubicin/curcumin-loaded copolymer/polymer nanoparticles are successful anticancer-targeted drug delivery system for effective cancer chemotherapy.**

Keywords— **magnetic nanoparticles, drug delivery systems, hyperthermia, magnetic resonance imaging.**

I. INTRODUCTION

Recent advances in nanotechnology have driven the development of multifunctional nanoparticles which are promissing for targeted delivery of both imaging and therapeutic agents in biomedical applications [1-3]. Among various materials used, magnetite nanoparticles (MNPs) have been proven to be an important lass of material thanks to their unique properties including the ablity to be guided by an external magnetic field, the ability to perturb magnetic local fields and the ability to create heat when subjected to an alternative magnetic field. Many researches have been carried out concerning the fabrication, characterization of the multifunctional nanosystems based on magnetite nanoparticles as core and polymers as shell layer with targeting moiety for selective delivery [4-7]. Besides,several polymeric nanosystems without the MNPs in the core have also paid much attention of researchers in the recent years. The micelles nanosystems which incorporate drugs such as paclitaxel, doxorubicin, curcumin in its hydrophobic domain and carry targeting and imaging moiety have tremendous potential in cancer therapy [8-10].

In this review, we will summarize the recent studies at the Laboratory of Biomedical Nanomaterials in fabrication of multifunctional nanosystems based on Fe_3O_4magnetic nanoparicles encapsulated with different polymers as well as the targeted drug delivery systems for effective cancer chemotherapy. The preliminary application of MNPs capped with natural or synthesized polymers, namely chitosan (CS), acrylic acid (PAA) and alginate (Alg), for optical and magnetic resonance imaging (MRI) and hyperthermia will be presented. Furthermore, the cellular uptake and apoptosis of anticancer-drugs nanoparicles with folate decoration will also be investigated.

II. MATERIALS AND METHODS

A. Magnetite Nanoparticles Based Nanosystems

The Fe_3O_4 and the poly (styrene – co – acrylic acid) copolymer (PAA) were synthesized through co-precipitation and polymerization, respectively before the encapsulation process. The Fe_3O_4@CS, Fe_3O_4@PAA and Fe_3O_4@Alg nanosystems were prepared through ex-situ process by mixing the MNPs and polymer under vigorous stirring for 48 hours. Then, curcumin (Cur) was preliminarily dissolved in ethanol and absorbed on the Fe_3O_4 surface to form multifunctional nanosystem. Several nanosystems with and without Cur were prepared for further studies. The procedures are described in more detail in [11-13]. The crystal, morphological and magnetic properties of the magnetite nanoparticles based nanosystems was thoroughly characterized.

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B. Polymeric Micelle Based Nanosystems

The copolymer PLA-TPGS or PLA-PEG was first synthesized through the ring-opening polymerization of PLA and TPGS in the presence of stannous octotate as catalyst.The targeted drug delivery systems of paclitaxel, doxorubicin, curcumin loaded copolymer nanoparticles were prepared by a modified solvent extraction/evaporation process and decorated by folic acid. More details of the synthesis procedure can be found in [14]. Surface morphology, size distribution, zeta potential and apoptosis of the polymeic nanoparticles were also investigated.

III. RESULTS AND DISCUSSIONS

As for the magnetite nanoparticles based nanosystem, the co-precipitatedFe_3O_4particles are of single phase with an average diameter of 15-20 nm and a saturation magnetization of 65-70 emu/g. The Fe_3O_4@CS, Fe_3O_4@PAA and Fe_3O_4@Alg nanoparticles are almost spherical with 50 nm in diameter and a slight decrease by 5% in magnetization. The coating layers of polymers were confirmed by the observation ofthe stretching bands of free carboxyl group (C = O) on the surface of the nanoparticles at 1702 cm^{-1} and 1750 cm^{-1} for Fe_3O_4@PAA and Fe_3O_4@Alg, correspondingly; while the characteristic vibrations of N-H group in Fe_3O_4@CS were observed at 1379 and 1604 cm^{-1}, respectively. The linking between Fe_3O_4 and the encapsulating polymers was verified by the appearance of peaks at 567, 575 and 574 cm^{-1} for Fe_3O_4@CS, Fe_3O_4@PAA and Fe_3O_4@Alg, respectively which are assigned to the stretching band of Fe – O – Fe vibration originally observed at 585 cm^{-1}. The magnetic inductive heating (MIH) experiments were carried out at a magnetic field of 236 kHz and 70 Oe (Fig. 1). It can be easily seen that both Fe_3O_4@CS,Fe_3O_4@PAA and Fe_3O_4@Alg exhibit quite high magnetic heating performance thus demonstrating a potential to be utilized as thermal nanoseeds for hyperthermia application.

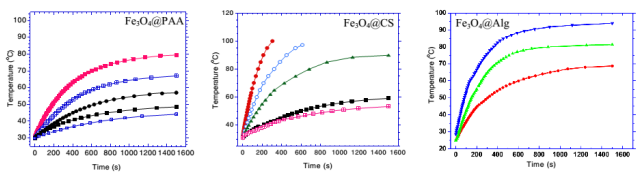

Fig. 1 Magnetic inductive heating curves ofFe_3O_4@CS, Fe_3O_4@PAA and Fe_3O_4@Alg nanosystems

In-vivo hyperthermia experiment was designed for the treatment of a Sarcoma tumor (6 × 6 mm2 size) using Fe_3O_4@PAA as a thermoseed (figure 2). As depicted by the images, all the tumor in the control mice increased continuously with time and the mice finally died 4 weeks after the experiment started (mouse A), whereas the tumor began to shrink after the first course of irraditaion by AC magnetic field and the mice were totally recovered 3 weeks after threee courses of treatment during the first week (mouse D).

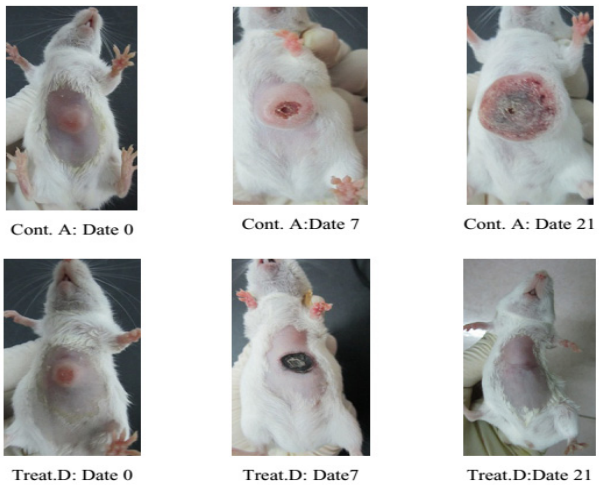

Fig. 2 Images of a control mouse (top) and the treated D mice (bottom) at three date periods

Figure 3 presents confocal microscope image of the macrophages alone and 1hour, 6 hours after its uptake with *Fe_3O_4@CS@Cur.* The conjugate evidenced by the green spots of Cur was observed to uptake in to the vacuole of the cells.From this result, one can deduce that the presence of Cur has created a wonderful enhancement in contrast of the imaging technique even at cellular level.

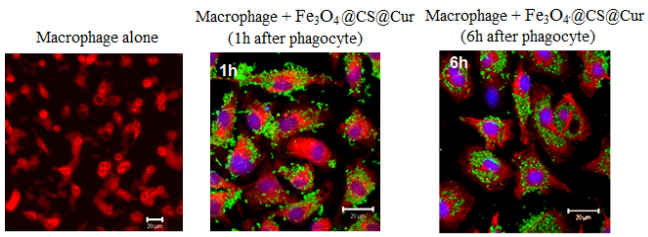

Fig. 3 Fluorescence images of macrophages alone, and macrophages with Fe_3O_4@CS@Cur 1 and 6 hours after phagocytosis

In the case of polymeric micelles based targeted drug delivery nanosystems, the obtained nanoparticles have spherical shape with an average diameter of around 50 nm. This small size makes them advantageous for the penetration to the cancer cells. The nanosystems were negatively charged with the zeta potential of about -30 mV thus proving the

stability of nanosystems. Thanks to the small size, drug-loaded polymeric micelle nanoparticles can penetrate through cell membrane, interfere in the metabolite action of the cells and cause cell death at last. As can be seen in fig. 4, the effect of paclitaxel loaded PLA-TPGS with folate decoration to Hela cancer cells significantly increases compared to that of paclitaxel loaded PLA-TPGS which is much higher than free paclitaxel. Moreover, the targeting effect of drug-loaded nanoparticles with folate decoration was also investigated *in-vitro* by the uptake of the nanosystem into cancer cell lines and *in-vivo* for nude mice. The results indicate that the targeted drug delivery systems based on polymeric micelles are effective approach for chemotherapy in cancer treatment.

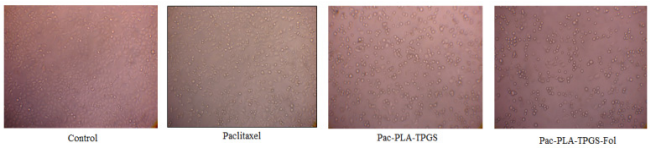

Fig. 4 Effect of Pac-PLA-TPGS and Pac-PLA-TPGS-Fol to Hela cancer cell line after 48h at concentration of 0.3 µg ml−1

IV. CONCLUSIONS

From all researches presented above, it can be summarized that: (i) several multifunctional nanosystems either with or without magnetite nanoparticles have been designed and successfully fabricated; (ii) magnetic nanoparticles based nanosystems exhibit to be a good candidate for both imaging and hyperthermia cancer treatment as well as for drug delivery systems; (iii) The targeted paclitaxel/doxorubicin/curcumin-loaded copolymer nanoparticles have been proven to be successful targeted anticancer-drug delivery systems for cancer chemotherapy.

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CONFLICT OF INTEREST

The authors declare that they have no conflict of interest.

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Author: Nguyen Xuan Phuc
Institute: Institute of Materials Science
Street: 18 Hoang Quoc Viet
City: Hanoi
Country: Vietnam
Email: phucnx@ims.vast.ac.vn