Promising results of application-oriented basic research on nanomedicine in Vietnam

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Abstract:

During the present decade application-oriented basic research on nanomedicine has rapidly developed in Vietnam. This work is a review of this development. It was directed towards following scientific topics: Biomedical utilization of PLA-TPGS and PLA-PEG, dendrimer-based anticancer drugs, special drug delivery nanosystems, various utilizations of nanocurcumin in nanomedicine, biomedical application of hydrogel nanocomposites, biosensors and biosensing methods, toxicity and antibacterial activity of different types of nanoparticles. Obtained scientific results demonstrated that although Vietnamese application-oriented basic research on nanomedicine began to develop only in this decade, it has achieved very promising successes.

Keywords: ***anticancer, biosensor, dendrimer, drug delivery, hydrogel.***

Classification numbers: ***5.1, 5.2, 5.4***

Introduction

At the beginning of present century the US President Bill Clinton has announced the National Nanotechnology Initiative NNI. Having been encouraged by this bright initiative, in the year 2002 Ministry of Science and Technology of Vietnam has decided to open a new prior interdisciplinary scientific direction, the Nanotechnology, in the National Basic Science Research Programme. The application of the a achievements of nanotechnology to medicine has resulted in the emergence of nanomedicine in Vietnam since the beginning of the present decade. The purpose of this work is to review the development application-oriented basic research on nanomedicine in Vietnam during this first decade.

The subsequent Section II is devoted to the review of the research on the use of poly(lactide)-d-α-tocopheryl poly(ethylene glycol) succinate (PLA-TPGS) and poly(lactide)-poly(ethylene glycol)(PLA-PEG) copolymers. Some special drug delivery nanosystems are presented in Section IV. The role of curcumin (Cur) is presented in Section V. Section VI is devoted to the review on biomedical applications of hydrogel composites. The content of Section VII is the presentation on biosensors

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and biosensing methods. The subject of Section VIII is the toxicity and antibacterial activity of some types of nanoparticles. The Conclusion and Discussion are presented in Section IX.

Biomedical ultilization of PLA-TPGS and PLA-PEG

The utilization of PLA-TPGS in nanomedicine began in Vietnam since 2012. Ha Phuong Thu, Le Mai Huong, et al. [1] studied apoptosis induced by PLA-TPGS in Hep-G2 cell.

Paclitaxel is an important anticancer drug in clinical use for treatment of a variety of cancers. The clinical application of paclitaxel in cancer treatment is considerably limited due to its serious poor delivery characteristics. In this study paclitaxel-loaded copolymer poly(lactide)-d-α-tocopheryl polyethylene glycol 1000 succinate (PLA-TPGS) nanoparticles were prepared by a modified solvent extraction/evaporation technique. The characteristics of the nanoparticles, such as surface morphology, size distribution, zeta potential, solubility and apoptosis were investigated *in vitro*. The obtained spherical nanoparticles were negatively charged with a zeta potential of about -18 mV with the size around 44 nm and a narrow size distribution. The ability of paclitaxel-loaded PLA-TPGS nanoparticles to induce apoptosis in human hepatocellular carcinoma cell line (Hep-G2) indicates the possibility of developing paclitaxel nanoparticles as a potential universal cancer chemotherapeutic agent.

Subsequently, *in vitro* apoptosis enhancement of Hep-G2 cells by PLA-TPGS and PLA-PEG block copopymer encapsulated Curcumin nanoparticles were investigated by Le Mai Huong, Ha Phuong Thu, et al. [2]. In this work nanodrug systems containing curcumin (Cur) encapsulated with block copolymers poly(lactide)-d-α-tocopheryl poly(ethylene glycol) 1000 succinate (PLA-TPGS) and poly(lactide)-poly(ethylene glycol) (PLA-PEG) were prepared and characterized by infrared and fluorescence spectroscopy, field-emission scanning electron microscopy (FE-SEM), and dynamic light scattering (DLS). Upon encapsulation, the highest solubility of Cur-PLA-TPGS and Cur-PLA-PGE dried powder was calculated as high as 2.40 and 2.20 mg ml^{-1}, respectively, an increase of about 350-fold compared to that of Cur (6.79 $\mu g\ ml^{-1}$). The antitumor assays (cytotoxic and antitumor-promoting assays) on Hep-G2 cells of copolymer-encapsulated Cur nanoparticles showed the apoptotic activity due to the remarkable changes in size, morphology, and angiogenesis ability of tumor cells in all cases of the tested samples as compared with the control.

In Ref. [3] Le Quang Huan, et al. investigated anti-tumor activity of docetaxel PLGA-PEG nanoparticle with a novel anti-HER2 single chain fragment (scF). The authors developed pegylated (poly(D,L-lactide-co-glycolide) (PLGA-PEG) nanoparticles for loading docetaxel and improving active target in cancer cells because they have advantages over other nanocarriers such as excellent biocompatibility, biodegradability and mechanical strength and these nanoparticles were conjugated with molecules of a novel anti-HER2 single chain fragment (scF) by a simple carbodiimide modified method. ScF have potential advantages over whole antibodies such as more rapid tumor penetration and clearance. In addition, to investigate cellular uptake of targeted nanocarriers, many studies have been performed by linking with fluorescent factors, but in this study 6-histidine-tag fused with novel anti-HER2 scF antibodies was used to purify protein and to study binding activity and cellular uptake of targeting nanoparticles. Furthermore, cytotoxicity of these nanoparticles was also investigated in BT474 (HER2 overexpress) and MDA-MB-231 (HER2 underexpress) cells.

In vitro and *in vivo* targeting effect of folate decorated paclitaxel loaded PLA-TPGS nanoparticles was investigated by Ha Phuong Thu, et al. [4]. The authors noted that paclitaxel is one of the most effective chemotherapeutic agents for treating various types of cancer. However, the clinical application of paclitaxel in cancer treatment is considerably limited due to its poor water solubility and low therapeutic index. Thus, it requires an urgent solution to improve therapeutic efficacy of paclitaxel. In this study folate decorated paclitaxel loaded PLA-TPGS nanoparticles were prepared by a modified emulsification/solvent evaporation method. The obtained nanoparticles were characterized by FESEM, Fourier transform infrared (FTIR) and DLS method. The spherical nanoparticles were around 50 nm in size with a narrow size distribution. Targeting effect of nanoparticles was investigated *in vitro* on cancer cell line and *in vivo* on tumor bearing nude mouse. The results indicated the effective targeting of folate decorated paclitaxel loaded copolymer nanoparticles on cancer cells both *in vitro* and *in vivo*.

In Ref. [5] Ha Phuong Thu, et al. studied enhanced cellular uptake and cytotoxicity of folate decorated doxorubicin (DOX) loaded PLA-TPGS nanoparticles. DOX is one of the most effective anticancer drugs for treating many types of cancer. However, the clinical applications of DOX were hindered because of serious side-effects resulting from the unselective delivery to cancer cell including congestive heart failure, chronic cardiomyopathy and drug resistance. Recently, it has been demonstrated that loading anti-cancer drugs onto drug delivery nanosystems helps to maximize therapeutic efficiency and minimize unwanted side-effects via passive and active targeting mechanisms. In this study the authors

prepared folate decorated DOX loaded PLA-TPGS nanoparticles with the aim of improving the potential as well as reducing the side-effects of DOX. Characteristics of nanoparticles were investigated by FESEM, DLS and FTIR. Anticancer activity of the nanoparticles was evaluated through cytotoxicity and cellular uptake assays on HeLa and HT29 cancer cell lines. The results showed that prepared drug delivery system had size around 100 nm and exhibited higher cytotoxicity and cellular uptake on both tested HeLa and HT29 cells.

Previous studies have been performed by linking with fluorescent factors, but in this study 6-histidine-tag fused with novel anti-HER2 scF antibodies was used to purify protein and to study binding activity and cellular uptake of targeting nanoparticles. Furthermore, cytotoxicity of these nanoparticles was also investigated in BT474 (HER2 overexpress) and MDA-MB-231 (HER2 underexpress) cells.

In Ref. [6] Ha Phuong Thu, et al. studied characteristics and cytotoxicity of folate-modified curcumin loaded PLA-PEG micellar nano systems with various PLA/PEG ratios. Targeting delivery system using natural drugs for tumor cells is an appealing platform help to reduce the side effects and to enhance the therapeutic effects of the drug. In this study, the authors synthesized curcumin (Cur) loaded Poly lactic - Poly ethylenglycol micelle (Cur/PLA-PEG) with the ratio of PLA/PEG of 3:1, 2:1, 1:1, 1:2 and 1:3 (w/w) and another micelle modified by folate (Cur/PLA-PEG-Fol) for targeting cancer therapy. The PLA-PEG copolymer was synthesized by ring opening polymerization method. After loading onto the micelle, solubility of Cur increased from 0.38 to 0.73 mg ml^{-1}. The average size of prepared Cur/PLA-PEG micelles was from 60 to 69 nm (corresponding to the ratio difference of PLA/PEG) and the drug encapsulating efficiency was from 48.8 to 91.3%. Compared with the Cur/PLA-PEG micelles, the size of Cur/PLA-PEG-Fol micelles were from 80 to 86 nm and showed better *in vitro* cellular uptake and cytotoxicity towards HepG2 cells. The cytotoxicity of the NPs, however, depends much on the PEG component. The results demonstrated that folate-modified micelles could serve as a potential nano carrier to improve solubility, anti-cancer activity of Cur and targeting ability of the system.

Targeted drug delivery nanosystems based on TPGS for cancer treatment were investigated by Ha Phuong Thu, et al. [7]. Along with the development of nanotechnology, drug delivery nanosystems (DDNSs) have attracted a great deal of concern among scientists over the world, especially in cancer treatment. DDNSs not only improve water solubility of anticancer drugs but also increase therapeutic efficacy and minimize the side effects of treatment methods through targeting mechanisms including passive and active targeting. Passive targeting is based on the nano-size of drug delivery systems while active targeting is based on the specific bindings between targeting ligands attached on the drug delivery systems and the unique receptors on the cancer cell surface. In this article the authors present some results in the synthesis and testing of DDNSs prepared from copolymer poly(lactide)-tocopheryl polyethylene glycol succinate (PLA-TPGS), which carry anticancer drugs including curcumin, paclitaxel and doxorubicin. In order to increase the targeting effect to cancer cells, active targeting ligand folate was attached to the DDNSs. The results showed copolymer PLA-TPGS to be an excellent carrier for loading hydrophobic drugs (curcumin and paclitaxel). The fabricated DDNSs had a very small size (50-100 nm) and enhanced the cellular uptake and cytotoxicity of drugs. Most notably, folate-decorated paclitaxel-loaded copolymer PLA-TPGS nanoparticles (Fol/PTX/PLA-TPGS NPs) were tested on tumor-bearing nude mice. During the treatment time, Fol/PTX/PLA-TPGS NPs always exhibited the best tumor growth inhibition compared to free paclitaxel and paclitaxel-loaded copolymer PLA-TPGS nanoparticles. All results evidenced the promising potential of copolymer PLA-TPGS in fabricating targeted DDNSs for cancer treatment.

Curcumin as fluorescent probe for directly monitoring *in vitro* uptake of curcumin combined paclitaxel loaded PLA-TPGS nanopartic was studied by Ha Phuong Thu, Hoang Thi My Nhung, et al. [8]. It was well-known that theranostics, which is the combination of both therapeutic and diagnostic capacities in one dose, is a promising tool for both clinical application and research. Although there are many chromophores available for optical imaging, their applications are limited due to the photobleaching property or intrinsic toxicity. Curcumin, a natural compound extracted from the rhizome of curcuma longa, is well known thanks to its bio-pharmaceutical activities and strong fluorescence as biocompatible probe for bio-imaging. In this study the authors aimed to fabricate a system with dual functions: diagnostic and therapeutic, based on poly(lactide)-tocopheryl polyethylene glycol succinate (PLA-TPGS) micelles co-loaded curcumin (Cur) and paclitaxel (PTX). Two kinds of curcumin nanoparticle (NP) were fabricated and characterized by FESEM and DLS methods. The cellular uptake and fluorescent activities of curcumin in these systems were also tested by bioassay studies, and were compared with paclitaxe-oregon. The results showed that (Cur + PTX)-PLA-TPGS NPs is a potential system for cancer theranostics.

In Ref. [9] Le Quang Huan, et al. evaluated anti-HER2 scFv-conjugated

PLGA-PEG nanoparticles on tumor-spheroids of BT474 and HCT116 cancer cells. The authors noted that three-dimensional culture cells (spheroids) are one of the multicellular culture models that can be applied to anticancer chemotherapeutic development. Multicellular spheroids more closely mimic in vivo tumor-like patterns of physiologic environment and morphology. In previous research, the authors designed docetaxel-loaded pegylated poly(D, L-lactide-co-glycolide) nanoparticles conjugated with anti-HER2 single chain antibodies (scFv-DOX-PLGA-PEG) and evaluated them in 2D cell culture. In this study, they continuously evaluate the cellular uptake and cytotoxic effect of scFv-DOX-PLGA-PEG on a 3D tumor spheroid model of BT474 (HER2-overexpressing) and HCT116 (HER2-underexpressing) cancer cells. The results showed that the nanoparticle formulation conjugated with scFv had a significant internalization effect on the spheroids of HER2-overexpressing cancer cells as compared to the spheroids of HER2-underexpressing cancer cells. Therefore, cytotoxic effects of targeted nanoparticles decreased the size and increased necrotic score of HER2-overexpressing tumor spheroids. Thus, these scFv-DOX-PLGA-PEG nanoparticles have potential for active targeting for HER2-overexpressing cancer therapy. In addition, BT474 and HCT116 spheroids can be used as a tumor model for evaluation of targeting therapies.

In vitro evaluation of Aurora kinase inhibitor VX680 in formulation of PLA-TPGS nanoparticles was performed by Hoang Thi My Nhung, et al. [10]. In this work polymeric nanoparticles prepared from poly(lactide)-tocopheryl polyethylene glycol succinate (PLA-TPGS) were used as potential drug carries with many advantages to overcome the disadvantages of insoluble anticancer drugs and enhance blood circulation time and tissues. VX680 is an Aurora kinase inhibitor and is also the foremost Aurora kinase inhibitor to be studied in clinical trials. In this study, the authors aimed to investigate whether VX680-loaded PLA-TPGS nanoparticles (VX680-NPs) are able to effectively increase the toxicity of chemotherapy. Accordingly, the authors first synthesized VX680-loaded nanoparticles and NP characterizations of morphology, mean size, zeta potential, and encapsulation efficiency were spherical shape, 63 nm, -30 mV and 76%, respectively. Then, they investigated the effects on HeLa cells. The cell cytotoxicity was evaluated by the xCELLigence real-time cell analyzer allowing measurement of changes in electrical impedance on the surface of the E-plate. Analysis of nucleus morphology and level of histone H3 phosphorylation was observed by confocal fluorescence scanning microscopy. Cell cycle distribution and apoptosis were analyzed by flow cytometry. The results showed that VX680-NPs reduced cell viability with half maximal inhibitory concentration (IC_{50}) value lower 3.4 times compared to free VX680. Cell proliferation was inhibited by VX680-NPs accompanied by other effects such as high abnormal changes of nucleus, a decrease of phospho-histone H3 at Ser10 level, an increase of polyploid cells and resulted in higher apoptotic cells. These results demonstrated that VX680-NPs had more cytotoxicity than as treated with VX680 alone. Thus, VX680-NPs may be considered as promising drug delivery system for cancer treatment.

Dendrimer-based anticancer drugs

The demonstration of a high efficiency for loading and releasing dendrimer-based anticancer drugs against cancer cells *in vitro* and *in vivo* was performed by Tran Ngoc Quyen, Nguyen Cuu Khoa, et al. [11]. In this work pegylated polyamidoamine (PAMAM) dendrimer at generation 3.0 (G 3.0) and carboxylated PAMAM dendrimer G 2.5 were prepared for loading anticancer drugs. For loading cisplatin, carboxylated dendrimer could carry 26.64 wt/wt% of cisplatin. The nanocomplexes have size ranging from 10 to 30 nm in diameter. The drug nanocarrier showed activity against NCI-H460 lung cancer cell line with IC_{50} of 23.11±2.08 μg ml^{-1}. Pegylated PAMAM dendrimers (G 3.0) were synthesized below 40 nm in diameter for carrying 5-fluorouracil (5-FU). For 5-FU encapsulation, pegylated dendrimer showed a high drug-loading efficiency of the drug and a slow release profile of 5-FU. The drug nanocarrier system exhibited an antiproliferative activity against MCF-7 cells (breast cancer cell) with a IC_{50} of 9.92±0.19 μg ml^{-1}. *In vivo* tumor xenograft study showed that the 5-FU encapsulated pegylation of dendrimer exhibited a significant decrement in volume of tumor which was generated by MCF-7 cancer cells. The positive results from this study our studies could pave the ways for further research of drugs dendrimer nanocarriers toward cancer chemotherapy.

Cationic dendrimer-based hydrogels for controlled heparin release were prepared by Nguyen Cuu Khoa, Tran Ngoc Quyen, et al. [12]. In this work the authors introduced a PAMAM dendrimers and tetronic (Te) based hydrogels in which precursor copolymers were prepared with simple methods. In the synthetic process, tyramine-conjugated tetronic (TTe) was prepared via activation of its four terminal hydroxyl groups by nitrophenyl chloroformate (NPC) and then substitution of tyramine (TA) into the activated product to obtain TTe. Cationic PAMAM dendrimers G3.0 functionalized with p-hydroxyphenyl acetic acid (HPA) by use of carbodiimide coupling agent (EDC) to obtain Den-HPA. Proton nuclear magnetic

resonance (^{1}H-NMR) spectroscopy confirmed the amount of HPA and thermal analysis conjugations. The aqueous TTe and Den-HPA copolymer solution rapidly formed the cationic hydrogels in the presence of horseradish peroxidase enzyme (HRP) and hydrogen peroxide (H_2O_2) at physiological conditions. The gelation time of the hydrogels could be modulated ranging from 7 to 73 secs, when the concentrations of HRP and H_2O_2 varied. The hydrogels exhibited minimal swelling degree and low degradation under physical condition. *In vitro* cytotoxicity study indicated that the hydrogels were highly cytocompatible as prepared at 0.15 mg ml^{-1} HRP and 0.063 wt% of H_2O_2 concentration. Heparin release profiles show that the cationic hydrogels can sustainably release the anionic anticoagulant drug. The obtained results demonstrated a great potential of the cationic hydrogels for coating medical devices or delivering anionic drugs.

In Ref. [13] Nguyen Cuu Khoa, Tran Ngoc Quyen, et al. applied ^{1}H-NMR spectroscopy as an effective method for predicting molecular weight of polyaminoamine dendrimers and their derivatives. They have established two formulas to predict molecular weight of polyaminoamine dendrimers and their alkylated derivatives, based on the theoretical number of protons at specific positions in the dendrimers and the true value of the integral values of these protons appearing in proton nuclear magnetic resonance spectra. Calculated results indicated that molecular weight of the dendrimers is approximately equal to results from mass spectrometry. Degrees of alkylation were easily calculated for each dendrimer-alkylated derivative. According to the obtained results, the authors confirm that the use of the proton spectra can be an effective method to predict molecular weight of dendrimers.

An improved method for preparing cisplatin-dendrimer nanocomplex and its behavior against NCI-H460 lung cancer cell were investigated by Tran Ngoc Quyen, Nguyen Cuu Khoa, et al. [14]. The effect of anticancer drugs could be significantly enhanced if it is encapsulated in drug delivery vehicles such as liposomes, polymers, dendrimers and other materials. For some conventional cisplatin encapsulating methods, however, suffers from low loading efficiency. Therefore, in order to overcome this limitation, in this study sonication was used in preparation of the nanocomplex of a species of aquated cisplatin and carboxylated PAMAM dendrimer G3.5 to evaluate loading capacity as well as plantinum release behavior using FTIR, UV-Vis, NMR, inductively coupled plasma atomic absorption spectroscopy (ICP-AES), and transmission electron microscopy (TEM). The results showed that 25.20 and 27.83 wt/wt% of cisplatin were loaded under stirring and sonication respectively, a remarkably improvement in loading efficiency compared to that of conventional method that used of cisplatin. *In vitro* study showed that this drug-nanocarrier complex also help reduce cisplatin's cytotoxicity but can still keep sufficient antiproliferative activity against lung cancer cell, NCI-H460, with IC_{50} at 0.985±0.01 μM.

Highly lipophilic pluronics-conjugated polyamidoamine dendrimer nanocarriers as potential delivery system for hydrophobic drug were investigated by Nguyen Cuu Khoa, Tran Ngoc Quyen, et al. [15]. In this work four kinds of pluronics (P123, F68, F127 and F108) with varying hydrophilic-lipophilic balance (HLB) values were modified and conjugated on 4th generation of dendrimer PAMAM. The obtained results from FTIR, ^{1}H-NMR, gel permeation chromatography (GPC) showed that the pluronics effectively conjugated on the dendrimer. The molecular weight of four PAMAM G4.0-Pluronics and its morphologies are in range of 200.15-377.14 KDa and around 60-180 nm in diameter by TEM, respectively. Loading efficiency and release of hydrophobic fluorouracil (5-FU) anticancer drug were evaluated by high performance liquid chromatography (HPLC). Interesting that the dendrimer nanocarrier was conjugated with a highest lipophilic pluronic P123 (G4.0-P123) exhibiting a highest drug loading efficiency (up to 76.25%) in comparison with another pluronics. Live/dead fibroblast cell staining assay mentioned that all conjugated nanocarriers are highly biocompatible. The drug-loaded nanocarriers also indicated a highly anti-proliferative activity against MCF-7 breast cancer cell. The obtained results demonstrated a great potential of the highly lipophilic pluronics-conjugated nanocarriers in hydrophobic drugs delivery for biomedical applications.

Special drug delivery nanosystems

In Ref. [16] Nguyen To Hoai, Dang Mau Chien, et al. attempted to fabricate a nanoparticle formulation of ketoprofen (Keto)-encapsulated cucurbit [6] (CB [6]) uril nanoparticles, to evaluate its *in vitro* dissolution and to investigate its in vivo pharmaceutical property. The CB [6]-Keto nanoparticles were prepared by emulsion solvent evaporation method. Morphology and size of the successfully prepared nanoparticles were then confirmed using a transmission electron microscope and dynamic light scattering. It was shown that they are spherical with hydrodynamic diameter of 200-300 nm. The *in vitro* dissolution studies of CB [6]. Keto nanoparticles were conducted at pH 1.2 and 7.4. The results indicated that there is a significant increase in Keto concentration at pH 7.4 compared to pH 1.2. For the *in vivo* assessment, CB [6]. Keto nanoparticles and referential profenid were administered by oral gavages to rabbits. The results implied that CB[6]-Keto nanoparticles remarkably increased area under the

curve compared to profenid.

As new copolymer material for oral delivery of insulin Ho Thanh Ha, Dang Mau Chien, et al. [17] used poly(ethylene glycol)-grafted chitosan. In this work a new scheme of grafting poly (ethylene glycol) onto chitosan was proposed in this study to give new material for delivery of insulin over oral pathway. First, methoxy poly(ethylene glycol) amine (mPEGa MW 2000) were grafted onto chitosan (CS) through multiples steps to synthesize the grafting copolymer PEG-g-CS. After each synthesis step, chitosan and its derivatives were characterized by FTIR, ^{1}H-NMR Then, insulin loaded PEG-g-CS nanoparticles were prepared by cross-linking of CS with sodium tripolyphosphate (TPP). Same insulin loaded nanoparticles using unmodified chitosan were also prepared in order to compare with the modified ones. Results showed better protecting capacity of the synthesized copolymer over original CS. CS nanoparticles (10 nm of size) were gel like and high sensible to temperature as well as acidic environment while PEG-g-CS nanoparticles (200 nm of size) were rigid and more thermo and pH stable.

Targeted drug delivery nanosystems based on poly(lactide)-tocopheryl polyethylene glycol succinate for cancer treatment were studied by Ha Phuong Thu, et al. [18]. The authors noted that along with the development of nanotechnology, drug delivery nanosystems (DDNSs) have attracted a great deal of concern among scientists over the world, especially in cancer treatment. DDNSs not only improve water solubility of anticancer drugs but also increase therapeutic efficacy and minimize the side effects of treatment methods through targeting mechanisms including passive and active targeting. Passive targeting is based on the nano-size of drug delivery systems while active targeting is based on the specific bindings between targeting ligands attached on the drug delivery systems and the unique receptors on the cancer cell surface. In this article the authors present some of our results in the synthesis and testing of DDNSs prepared from copolymer poly(lactide)-tocopheryl polyethylene glycol succinate (PLA-TPGS), which carry anticancer drugs including curcumin, paclitaxel and doxorubicin. In order to increase the targeting effect to cancer cells, active targeting ligand folate was attached to the DDNSs. The results showed copolymer PLA-TPGS to be an excellent carrier for loading hydrophobic drugs (curcumin and paclitaxel). The fabricated DDNSs had a very small size (50-100 nm) and enhanced the cellular uptake and cytotoxicity of drugs. Most notably, folate-decorated paclitaxel-loaded copolymer PLA-TPGS nanoparticles (Fol/PTX/PLA-TPGS NPs) were tested on tumor-bearing nude mice. During the treatment time, Fol/PTX/PLA-TPGS NPs always exhibited the best tumor growth inhibition compared to free paclitaxel and paclitaxel-loaded copolymer PLA-TPGS nanoparticles. All results evidenced the promising potential of copolymer PLA-TPGS in fabricating targeted DDNSs for cancer treatment.

Chitosan-grafted pluronic® F127 copolymer nanoparticles containing DNA aptamer for PTX delivery to treat breast cancer cells were investigated by Nguyen Kim Thach, Le Quang Huan, et al. [19]. It was well-known that HER-2/ErbB2/Neu(HER-2), a member of the epidermal growth factor receptor family, is specifically overexpressed on the surface of breast cancer cells and serves a therapeutic target for breast cancer. In this study, the authors aimed to isolate DNA aptamer (Ap) that specifically bind to a HER-2 overexpressing SK-BR-3 human breast cancer cell line, using SELEX strategy. They developed a novel multifunctional composite micelle with surface modification of Ap for targeted delivery of paclitaxel. This binary mixed system consisting of Ap modified pluronic®F127 and chitosan could enhance PTX loading capacity and increase micelle stability. Polymeric micelles had a spherical shape and were self-assemblies of block copolymers of approximately 86.22±1.45 nm diameter. PTX could be loaded with high encapsulation efficiency (83.28±0.13%) and loading capacity (9.12±0.34%). The release profile were 29-35% in the first 12 h and 85-93% after 12d at pH 7.5 of receiving media. The IC_{50} doses by (3-(4,5-dimethylthiazol-2-yl) 2,5 dimethyltetrazolium bromide) (MTT) assay showed the greater activity of nanoparticles loaded paclitaxel over free paclitaxel and killed cells up to 95% after 6 h. These results demonstrated unique assembly with the capacity to function as an efficient detection and delivery vehicle in the biological living system.

In Ref. [20] Nguyen Tuan Anh, Dang Mau Chien, et al. demonstrated micro and nano liposome vesicles containing curcumin for using as a drug delivery system. In this work micro and nano liposome vesicles were prepared using a lipid film hydration method and a sonication method. Phospholipid, cholesterol and curcumin were used to form micro and nano liposomes containing curcumin. The size, structure and properties of the liposomes were characterized by using optical microscopy, TEM, UV-Vis and Raman spectroscopy. It was found that the size of the liposomes was dependent on their composition and the preparation method. The hydration method created micro multilamellars, whereas nano unilamellars were formed using the sonication method. By adding cholesterol, the vesicles of the liposome could be stabilized and stored at 4°C for up to 9 months. The liposome vesicles containing curcumin with good biocompatibility and biodegradability could be used for drug delivery applications.

Hierarchical self-assembly of heparin-PEG end-capped porous silica as a redox sensitive nanocarrier for doxorubicin delivery was demonstrated by Nguyen Cuu Khoa, Nguyen Dai Hai, et al. [21]. The authors noted that porous nanosilica (PNS) has been attracting a great attention in fabrication carriers for drug delivery system (DDS). However, unmodified PNS-based carriers exhibited the initial burst release of loaded bioactive molecules, which may limit their potential clinical application. In this study the surface of PNS was conjugated with adamantylamine (A) via disulfide bonds (PNS-SS-A) which was functionalized with cyclodextrin-heparin-polyethylene glycol (CD-HPEG) for redox triggered doxorubicin (DOX) delivery. The modified PNS was successfully formed with spherical shape and diameter around 50 nm determined by TEM. DOX was efficiently trapped in the PNS-SS-A@CD-HPEG and slowly released in phosphate buffered saline (PBS) without any initial burst effect. Importantly, the release of DOX was triggered due to the cleavage of the disulfide bonds in the presence of dithiothreitol (DTT). In addition, the MTT assay data showed that PNS-SS-A@CD-HPEG was a biocompatible nanocarrier and reduced the toxicity of DOX. These results demonstrated that PNS-SS-A@CD-HPEG has great potential as a novel nanocarrier for anticancer drug in cancer therapy.

Various utilizations of nanocurcumin in nanomedicine

In Section II we have presented the combinations of curcumin with paclitaxel loaded PLA-TPGS nanoparticles, PLA-PEG micellar nanosystems and PLA-TPGS and PLA-PEG block copolymer. In Section IV the micro and nano liposome vesicles drug delivery system containing curcumin was also presented. Beside above-mentioned combinations containing curcumin there are other biomedical utilizations of nanocurcumin. In Ref. [22] Le Mai Huong, Ha Phuong Thu et al. investigated antitumor activity of curcumin encapsulated by 1,3-β-glucan isolated from Vietnam medicinal mush room *Hericium erinaceum*. It was known that the clinical application of curcumin in cancer treatment is considerably limited due to its serious poor delivery characteristics. In order to increase the hydrophilicity and drug delivery capability, the authors encapsulated curcumin into 1,3-β-glucan isolated from Vietnam medicinal mushroom *Hericium erinaceum*. The 1,3-β-glucan-encapsulated curcumin nanoparticles (Cur–Glu) were found to be spherical with an average size of 50 nm, being suitable for drug delivery applications. They were much more soluble in water not only than free curcumin but also than other biodegradable polymer-encapsulated curcumin nanoparticles. An antitumor-promoting assay was carried out, showing the positive effects of Cur-Glu on tumor promotion of Hep-G2 cell line *in vitro*.

Folate attached, curcumin loaded Fe_3O_4 nanoparticles as a novel multifunctional drug delivery system for cancer treatment were prepared and investigated by Ha Phuong Thu, Nguyen Xuan Phuc, et al. [23]. In this work the authors studied the role of folic acid as a targeting factor on magnetic nanoparticle Fe_3O_4 based curcumin loading nanosystem. Characteristics of the nanosystems were investigated by FTIR and FESEM, X-ray diffraction (XRD), thermal gravimetric analysis (TGA) and vibrating sample magnetometer (VSM), while targeting role of folic was accessed in vivo on tumor bearing mice. The results showed that folate attached Fe_3O_4 based curcumin loading nanosystem has very small size and exhibits better targeting effect compared to the counterpart without folate. In addition, magnetic induction heating of this nanosystem evidenced its potential for cancer hyperthermia.

In Ref. [24] Ha Phuong Thu, Nguyen Xuan Phuc, et al. investigated Fe_3O_4/o-Carboxymethyl Chitosan/Curcumin-based nanodrug system for chemotherapy and fluorescence imaging in HT29 cancer cell line. In this work a multifunctional nanodrug system containing Fe_3O_4, o-carboxymethyl chitosan (OCMCs), and curcumin (Cur) has been prepared and characterized by infrared and fluorescence spectroscopy, XRD and FE-SEM. The fluorescent staining experiments showed that this system not only had no effect on the cell internalization ability of curcumin but also successfully led curcumin into the HT29 cells as expected. From real-time cell analysis (RTCA), the effect of Fe_3O_4/OCMCs/Cur on this cancer cell line was found to be much stronger than that of pure curcumin. This system contained magnetic particles and, therefore, could be also considered for hyperthermia therapy in cancer treatment.

A novel nanofiber curcumin-loaded polylactic acid constructed by electrospinning was investigated by Mai Thi Thu Trang, Tran Dai Lam, et al. [25]. Curcumin (Cur), extracted from the *Curcuma longa* L. plant, is well known for its anti-tumor, anti-oxidant, anti-inflammatory and anti-bacterial properties. Nanofiber mats of polylactic acid (PLA) loading Cur (5 wt%) were fabricated by electrospinning (e-spinning). Morphology and structure of the fibers were characterized by FE-SEM and FTIR spectroscopy, respectively. The diameters of the obtained fibers varied from 200 to 300 nm. The release capacity of curcumin from curcumin-loaded PLA fibers was investigated in phosphate buffer saline (PBS) containing ethanol. After 24 h, 50% of the curcumin was released from curcumin-loaded PLA fibers. These results of electrospun (e-spun) fibers exhibit the potential for biomedical application.

In Ref. [26] Ha Phuong Thu, Nguyen Xuan Phuc, et al. prepared polymer-

encapsulated curcumin nanoparticles and investigated their anti-cancer activity. It is well-knows that curcumin (Cur) is a yellow compound isolated from rhizome of the herb curcuma longa. Curcumin possesses antioxidant, anti-inflammatory, anti-carcinogenic and antimicrobial properties, and suppresses proliferation of many tumor cells. However, the clinical application of curcumin in cancer treatment is considerably limited due to its serious poor delivery characteristics. In order to increase the hydrophilicity and drug delivery capability, the authors encapsulated curcumin into copolymer PLA-TPGS, 1,3-β-glucan (Glu), O-carboxymethyl chitosan (OCMCS) and folate-conjugated OCMCS (OCMCs-Fol). These polymer-encapsulated curcumin nanoparticles (Cur-PLA-TPGS, Cur-Glu, Cur-OCMCS and Cur-OCMCS-Fol) were characterized by infrared (IR), fluorescence (FL), photoluminescence (PL) spectra, FE-SEM, and found to be spherical particles with an average size of 50-100 nm, being suitable for drug delivery applications. They were much more soluble in water than not only free curcumin but also other biodegradable polymer-encapsulated curcumin nanoparticles. The anti-tumor promoting assay was carried out, showing the positive effects of Cur-Glu and Cur-PLA-TPGS on tumor promotion of Hep-G2 cell line *in vitro*. Confocal microscopy revealed that the nano-sized curcumin encapsulated by polymers OCMCS and OCMCS-Fol significantly enhanced the cellular uptake (cancer cell HT29 and HeLa).

Curcumin-loaded pluronic F127/ Chitosan nanoparticles for cancer therapy were prepared by Le Quang Huan, et al. [27]. In this work curcumin-loaded NPs have been prepared by an ionic gelation method using CS and pluronic®F-127 (PF) as carriers to deliver curcumin to the target cancer cells. Prepared NPs were characterized using Zetasizer, fluorescence microscopy, SEM and TEM. The results showed that the encapsulation efficiency of curcumin was approximately 50%. The average size of curcumin-loaded PF/CS NPs was 150.9 nm, while the zeta potential was 5.09 mV. Cellular uptake of curcumin-loaded NPs into HEK293 cells was confirmed by fluorescence microscopy.

In a subsequent work [28] Le Quang Huan, et al. investigated docetaxel and curcumin-containing poly(ethylene glycol)-block-poly(ε-caprolactone) polymer micells. In this work nanoparticles (NPs) prepared from poly(ethylene glycol)-block-poly (ε-caprolactone) (PEG–PCL) were fabricated by the modified nanoprecipitation method with and without sonication to entrap DOX and curcumin (Cur). NPs were characterized in terms of morphology, size distribution, zeta potential, encapsulation efficiency and cytotoxicity. The particles have a ~45-80 nm mean diameter with a spherical shape. The cellular uptake of the NPs was observed after 2 and 4 h of incubation by fluorescence of curcumin loaded with docetaxel. The cell viability was evaluated by an MTT assay on the Hela cell line. DOX and DOX-Cur NPs had higher cytotoxicity and a much lower IC_{50} value compared with free DOX or Cur after 24 and 48 h of incubation. Doc and Cur incorporated into the PEG-PCL NPs had the highest cytotoxicity in comparison with all other NPs and may be considered as an attractive and promising drug delivery system for cancer treatment.

Biomedical application of hydrogel nanocomposites

Tetronic-grafted chitosan hydrogel as an injectable and biocompatible scaffold for biomedical applications was investigated by Tran Ngoc Quyen, Nguyen Cuu Khoa, et al. [29]. In recent years, injectable chitosan-based hydrogels have been widely studied towards biomedical applications because of their potential performance in drug/cell delivery and tissue regeneration. In this study, the authors introduce a simple and organic solvent-free method to prepare tyramine tetronic-grafted chitosan (TTeCS) via activation of four terminal hydroxyl groups of tetronic, partial tyramine conjugate into the activated product and grafting remaining activated moiety of tetronic-tyramine onto chitosan. The grafted copolymer was well-characterized by UV-Vis, ^{1}H-NMR and TGA. The aqueous TTeC copolymer solution rapidly formed hydrogel in the presence of horseradish peroxidase (HRP) and hydrogen peroxide (H_2O_2) at physiological conditions. The gelation time of the hydrogel was performed within a time period of 4 to 60 sec when the concentrations of HRP, H_2O_2, and polymers varied. The hydrogel exhibited highly porous structure which could be controlled by using H_2O_2. *In vitro* cytotoxicity study with Human Foreskin Fibroblast cell using live/dead assay indicated that the hydrogel was high cytocompatibility and could play a role as a scaffold for cell adhesion. The injectable hydrogels didn't cause any inflammation after one day and 2 weeks of the *in vivo* injection. The obtained results demonstrated a great potential of the TTeCS hydrogel in biomedical applications.

Enzyme-mediated *in situ* preparation of biocompatible hydrogel composites from chitosan derivative and biphasic calcium phosphate nanoparticles for bone regeneration was performed by Nguyen Cuu Khoa, Tran Ngoc Quyen, et al. [30]. It was known that injectable chitosan-based hydrogels have been widely studied toward biomedical applications because of their potential performance in drug/cell delivery and tissue regeneration. In this study the authors introduce tetronic-grafted chitosan containing tyramine moieties which have been utilized for *in situ* enzyme-mediated hydrogel preparation. The hydrogel can be used

to load nanoparticles (NPs) of biphasic calcium phosphate (BCP), mixture of hydroxyapatite (HAp) and tricalcium phosphate (TCP), forming injectable biocomposites. The grafted copolymers were well-characterized by ^{1}H-NMR. BCP nanoparticles were prepared by precipitation method under ultrasonic irradiation and then characterized by using XRD and SEM. The suspension of the copolymer and BCP nanoparticles rapidly formed hydrogel biocomposite within a few seconds of the presence of HRP and H_2O_2. The compressive stress failure of the wet hydrogel was at 591±20 KPa with the composite 10 wt% BCP loading. *In vitro* study using mesenchymal stem cells showed that the composites were biocompatible and cells are well-attached on the surfaces.

Fabrication of hyaluronan-poly(vinylphosphonic acid)-chitosan hydrogel for wound healing application was performed by Nguyen Dai Hai, Bui Chi Bao, et al. [31]. In this work new hydrogel made of hyaluronan, poly(vinylphosphonic acid), and chitosan (HA/PVPA/CS hydrogel) was fabricated and characterized to be used for skin wound healing application. Firstly, the component ratio of hydrogel was studied to optimize the reaction effectiveness. Next, its microstructure was observed by light microscope. The chemical interaction in hydrogel was evaluated by NMR spectroscopy and FTIR spectroscopy. Then, a study on its degradation rate was performed. After that, antibacterial activity of the hydrogel was examined by agar diffusion method. Finally,in vivostudy was performed to evaluate hydrogel's biocompatibility. The results showed that the optimized hydrogel had a threedimensional highly porous structure with the pore size ranging from about 25 μm to less than 125 μm. Besides, with a degradation time of two weeks, it could give enough time for the formation of extracellular matrix framework during remodeling stages. Furthermore, the antibacterial test showed that hydrogel has antimicrobial activity against E. coli. Finally, *in vivo* study indicated that the hydrogel was not rejected by the immune system and could enhance wound healing process. Overall, HA/PVPA/CS hydrogel was successfully fabricated and results implied its potential for wound healing applications.

In Ref. [32] injectable hydrogel composite based gelatin-PEG and biphasic calcium phosphate nanoparticles for bone regeneration was prepared by Nguyen Cuu Khoa, Tran Dai Lam, et al. Gelatin hydrogels have recently attracted much attention for tissue regeneration because of their biocompatibility. In this study the authors introduce polyethylene glycol (PEG)-grafted gelatin containing tyramine moieties which have been utilized for *in situ* enzyme-mediated hydrogel preparation. The hydrogel can be used to load nanoparticles of biphasic calcium phosphate, a mixture of hydroxyapatite and b-tricalcium phosphate, and forming injectable bio-composites. ^{1}H-NMR spectra indicated that tyramine-functionalized polyethylene glycol-nitrophenyl carbonate ester was conjugated to the gelatin. The hydrogel composite was rapidly formed *in situ* (within a few seconds) in the presence of horseradish peroxidase and hydrogen peroxide. *In vitro* experiments with biomineralization on the hydrogel composite surfaces was well-observed after 2 weeks soaking in simulated body fluid solution. The obtained results indicated that the hydrogel composite could be a potential injectable material for bone regeneration.

Biosensors and biosensing methods

Biosensor for cholesterol detection using interdigitated electrodes based on polyaniline-carbon nanotube film was demonstrated by Tran Dai Lam, et al. [33]. In this work polyaniline-carboxylic multiwalled carbon nanotubes composite film (PANi-MWCNT) has been polymerized on the surface of interdigitated platinum electrode (fabricated by MEMS technology) which was compatibly connected to Autolab interface via universal serial bus (USB). An amperometric biosensor based on covalent immobilization of cholesterol oxidase (ChOx) on PANi–MWCNT film with potassium ferricyanide (FeCN) as the redox mediator was developed. The mediator helps to shuttle the electrons between the immobilized ChOx and the PANi-MWCNT electrode, therefore operating at a low potential of -0.3 V compared to the saturated calomel electrode (SCE). This potential precludes the interfering compounds from oxidization. The bio-electrode exhibits good linearity from 0.02 to 1.2 mM cholesterol concentration with a correlation coefficient of 0.9985.

Electrochemical immunosensors based on different serum antibody immobilization methods for detection of Japanese encephalitis virus was developed by Tran Quang Huy, Nguyen Thi Hong Hanh, et al. [34]. In this work the authors described the development of electrochemical immunosensors based on human serum antibodies with different immobilization methods for detection of Japanese encephalitis virus (JEV). Human serum containing anti-JEV antibodies was used to immobilize onto the surface of silanized interdigitated electrodes by four methods: direct adsorption (APTES-serum), covalent binding with a cross linker of glutaraldehyde (APTES-GA-serum), covalent binding with a cross linker of glutaraldehyde combined with anti-human IgG (APTES-GA-anti-HIgG-serum) and covalent binding with a cross linker of glutaraldehyde combined with a bioaffinity of protein A (APTES-GA-PrA-serum). Atomic force microscopy was used to verify surface characteristics of the interdigitated electrodes before and after treatment with serum antibodies. The output signal of the immunosensors was measured by

the change of conductivity resulting from the specific binding of JEV antigens and serum antibodies immobilized on the electrodes, with the help of horseradish peroxidase (HRP)-labeled secondary antibody against JEV. The results showed that the APTES-GA-PrA-serum method provided the highest signal of the electrochemical immunosensor for detection of JEV antigens, with the linear range from 25 ng ml^{-1} to 1 µg ml^{-1}, and the limit of detection was about 10 ng ml^{-1}. This study showed a potential development of novel electrochemical immunosensors applied for virus detection in clinical samples in case of possible outbreaks.

Graphene patterned polyaniline-based biosensor for glucose detection was fabricated by Nguyen Van Chuc, Tran Dai Lam, et al. [35]. In this work a glucose electrochemical biosensor was layer-by-layer fabricated from graphene and polyaniline films. Graphene sheets (0.5×0.5 cm^2) with the thickness of 5 nm (15 layers) were synthesized by thermal chemical vapor deposition (CVD) under ambient pressure on copper tapes. Then they were transferred into integrated Fe_3O_4-doped polyaniline (PANi) based microelectrodes. The properties of the nanocomposite films were thoroughly characterized by SEM, Raman spectroscopy, atomic force microscopy (AFM) and electrochemical methods, such as square wave voltametry (SWV) and chronoamperometry. The above graphene patterned sensor (denoted as Graphene/Fe_3O_4/PANi/GOx) shows much improved glucose sensitivity (as high as 47 µA mM^{-1} cm^{-2}) compared to a non-graphene one (10 - 30 µA mM^{-1} cm^{-2}, as previously reported in the literature). It can be expected that this proof-of-concept biosensor could be extended for other highly sensitive biodetection.

Preparation of a fluorescent label tool based on lanthanide nanophosphor for viral biomedical application was performed by Le Quoc Minh, et al. [36]. In this article the authors reported the preparation of luminescent lanthanide nanomaterial (LLN) linked bioconjugates and their application as a label tool for recognizing virus in the processing line of vaccine industrial fabrication. Several LLNs with the nanostructure forms of particles or rods/wires with europium(III) and terbium(III) ions in lattices of vanadate, phosphate and metal organic complex were prepared to develop novel fluorescent conjugates able to be applied as labels in fluorescence immunoassay analysis of virus/vaccine.

In Ref. [37] Tran Hong Nhung, et al. synthesized dye-doped water soluble silica-based nanoparticles to label bacteria *E. coli* O157:H7 and investigated their photophysical properties. In this work organically modified silicate (ORMOSIL) nanoparticles (NPs) doped with rhodamine 6G and rhodamine B (RB) dyes were synthesized by Stöber method from methyltriethoxysilane $CH_3Si(OCH_3)_3$ precursor (MTEOS). The NPs are surface functionalized by cationic amino groups. The optical characterization of dye-doped ORMOSIL NPs was studied in comparison with that of free dye in solution. The synthesized NPs were used for labeling bacteria *E. coli* O157:H7. The number of bacteria have been counted using the fluorescent spectra and microscope images of labeled bacteria. The results show the ability of NPs to work as biomarkers.

The fabrication of the layer-by-layer biosensor using graphene films and the application for cholesterol determination were performed by Nguyen Van Chuc, et al. [38]. In this work the preparation and characterization of graphene films for cholesterol determination are described. The graphene films were synthesized by thermal chemical vapor deposition (CVD) method. Methane gas (CH_4) and copper tape were used as carbon source and catalyst in the graphene growth process, respectively. The intergrated array was fabricated by using micro-electro-mechanical systems (MEMS) technology in which Fe_3O_4-doped polyaniline (PANi) film was electropolymerized on Pt/Gr electrodes. The properties of the Pt/Gr/PANi/ Fe_3O_4 films were investigated by FE-SEM, Raman spectroscopy and electrochemical techniques. Cholesterol oxidase (ChOx) has been immobilized onto the working electrode with glutaraldehyde agent. The cholesterol electrochemical biosensor shows high sensitivity (74 µA mM^{-1} cm^{-2}) and fast response time (<5 s). A linear calibration plot was obtained in the wide cholesterol concentration range from 2 to 20 mM and correlation coefficient square (R2) of 0.9986. This new layer-by-layer biosensor based on graphene films promises many practical applications.

Electrosynthesis of polyaniline-multiwalled carbon nanotube nanocomposite films in the presence of sodium dodecyl sulfate for glucose biosensing was performed by Tran Dai Lam, et al. [39]. In this work polyaniline-mutilwalled carbon nanotube (PANi-MWCNT) nanocomposites were electropolymerized in the presence of sodium dodecyl sulfate (SDS) onto interdigitated platinum-film planar microelectrodes (IDµE). The MWCNTs were first dispersed in SDS solution then mixed with aniline and H_2SO_4. This mixture was used to electro-synthesize PANi-MWCNT films with potentiostatic method at E = +0.90 V (versus SCE). The PANi-MWCNT films were characterized by cyclic voltammetry (CV) and SEM. The results show that the PANi-MWCNT films have a high electroactivity, and a porous and branched structure that can increase the specific surface area for biosensing application. In this work the PANi-MWCNT films were applied for covalent immobilization of glucose oxidase (GOx) via glutaraldehyde agent. The GOx/PANi-MWCNT/IDµE

was studied using cyclic voltammetric and chronoamperometric techniques. The effect of several interferences, such as ascorbic acid (AA), uric acid (UA), and acetaminophen (AAP) on the glucosensing at +0.6 V (versus SCE) is not significant. The time required to reach 95% of the maximum steady-state current was less than 5 s. A linear range of the calibration curve for the glucose concentration lies between 1 and 12 mM which is a suitable level in the human body.

In Ref. [40] Ngo Vo Ke Thanh, et al. demonstrated a quartz crystal microbalance (QCM) as biosensor for detecting *Escherichia coli* O157:H7. The anti-*E. coli* O157:H7 antibodies were immobilized on a self-assembly monolayer (SAM) modified 5 MHz AT-cut quartz crystal resonator. The SAMs were activated with 16-mercaptopropanoic acid, in the presence of 1-ethyl-3-(3-dimethylaminopropyl) carbodiimide (EDC) and ester N-hydroxysuccinimide (NHS). The result of changing frequency due to the adsorption of *E. coli* O157:H7 was measured by the QCM biosensor system designed and fabricated by ICDREC-VNUHCM. This system gave good results in the range of 10^2-10^7 CFU ml^{-1} *E. coli* O157:H7. The time of bacteria *E. coli* O157:H7 detection in the sample was about 50 minutes. Besides, QCM biosensor from SAM method was comparable to protein A method-based piezoelectric immunosensor in terms of the amount of immobilized antibodies and detection sensitivity.

A significant progress in the research on silica-based optical nanoparticles for biomedical application was achieved by Tran Hong Nhung, et al. [41]. This article is a review of their research results. Gold, dye-doped silica based and core-shell multifunctional multilayer (SiO_2/Au, Fe_3O_4/SiO_2, Fe_3O_4/SiO_2/Au) water-monodispersed nanoparticles were synthesized by chemical route and surface modified with proteins and biocompatible chemical reagents. The particles were conjugated with antibody or aptamer for specific detecting and imaging bacteria and cancer cells. The photothermal effects of gold nanoshells (SiO_2/Au and Fe_3O_4/SiO_2/Au) on cells and tissues were investigated. The nano silver substrates were developed for surface enhanced Raman scattering (SERS) spectroscopy to detect melamine.

The preparation of gold nanoparticles by microwave heating and the study the conjugate of gold nanoparticles with *E. coli* O157:H7 antibody were demonstrated by Ngo Vo Ke Thanh, et al. [42]. In this article the authors described a method for the low cost synthesis of gold nanoparticles using sodium citrate (Na_3Ct) reduction in chloroauric acid ($HauCl_4.3H_2O$) by microwave heating (diameter about 13-15 nm). Gold nanoparticles were functionalized with surface activation by 3-mercaptopropionic acid for attaching antibody. These nanoparticles were then reacted with anti-*E. coli* O157:H7, using N-hydroxy succinimide (NHS) and carbondimide hydrochloride (EDC) coupling chemistry. The product was characterized with UV-visible spectroscopy, FTIR spectroscopy and zeta potential. In addition, the binding of antibody-gold nanoparticles conjugates to *E. coli* O157:H7 was demonstrated using TEM.

Silicon nanowire sensor for detecting alpha-fetoprotein biomarker of liver cancer was fabricated by Pham Van Binh, Dang Mau Chien, et al. [43]. In this article the authors presented a facile technique that only uses conventional micro-techniques and two size-reduction steps to fabricate wafer-scale silicon nanowire (SiNW) with widths of 200 nm. Initially, conventional lithography was used to pattern SiNW with 2 μm width. Then the nanowire width was decreased to 200 nm by two size-reduction steps with isotropic wet etching. The fabricated SiNW was further investigated when used with nanowire field-effect sensors. The electrical characteristics of the fabricated SiNW devices were characterized and pH sensitivity was investigated. Then a simple and effective surface modification process was carried out to modify SiNW for subsequent binding of a desired receptor. The complete SiNW-based biosensor was then used to detect alpha-fetoprotein (AFP), one of the medically approved biomarkers for liver cancer diagnosis. Electrical measurements showed that the developed SiNW biosensor could detect AFP with concentrations of about 100 ng ml^{-1}. This concentration is lower than the necessary AFP concentration for liver cancer diagnosis.

Electrochemical aptasensor for detecting tetracycline in milk was demonstrated by Le Quang Huan, et al. [44]. In this article the authors developed a label-free aptasensor for electrochemical detection of tetracycline. According to the electrochemical impendence spectroscopy (EIS) analysis, there was a linear relationship between the concentration of tetracycline and the electron transfer resistance from 10 to 3000 ng ml^{-1} of the tetracycline concentration. The detection limit was 10 ng ml^{-1} in 15 min detection duration. The prepared aptasensor showed a good reproducibility with an acceptable stability in tetracycline detection. The recoveries of tetracycline in spiked milk samples were in the range of 88.1-94.2%. The aptasensor has sensitivity 98% and specificity of 100%.

Toxicity and antibacterial activity of different types of nanoparticles

Capping and *in vivo* toxicity studies of gold nanoparticles were performed by Tran Hong Nhung, et al. [45]. In this work water-dispersed colloidal gold nanoparticles (AuNPs) with

high concentration were synthesized from metal precursor $HauCl_4$. The bovine serum albumin (BSA) and heterobiofunctionalized thiol polyethylene glycol acid (HS-PEG-COOH) were used as biofunctionalized layers for the synthesized AuNPs. The BSA and HS-PEG-COOH bound to the AuNPs were characterized qualitatively and quantitatively by transmission electron microscope and UV-VS spectrophotometer. The fabricated BSA and HS-PEG-COOH-capped AuNPs were introduced in mouse to study its toxicity and its availability in the liver.

Colloidal silver nanoparticles for preventing gastrointestinal bacterial infections were investigated by Le Anh Tuan, Tran Quang Huy, et al. [46]. In this work the authors have demonstrated a powerful disinfectant ability of colloidal silver nanoparticles (NPs) for the prevention of gastrointestinal bacterial infections. The silver NPs colloid was synthesized by a UV-enhanced chemical precipitation. Two gastrointestinal bacterial strains of *Escherichia coli* (ATCC 43888-O157:k-:H7) and *Vibrio cholerae* (O1) were used to verify the antibacterial activity of the as-prepared silver NPs colloid by means of surface disinfection assay in agar plates and turbidity assay in liquid media. Transmission electron microscopy was also employed to analyze the ultrastructural changes of bacterial cells caused by silver NPs. Noticeably, our silver NPs colloid displayed a highly effective bactericidal effect against two tested gastrointestinal bacterial strains at a silver concentration as low as ~3 mg l^{-1}. More importantly, the silver NPs colloid showed an enhancement of antibacterial activity and long-lasting disinfectant effect as compared to conventional chloramin B (5%) disinfection agent. These advantages of the as-prepared colloidal silver NPs make them very promising for environmental treatments contaminated with gastrointestinal bacteria and other infectious pathogens. Moreover, the powerful disinfectant activity of silver-containing materials can also help in controlling and preventing further outbreak of diseases.

Antibacterial studies of silver core-chitosan shell nanoparticles using catechol-functionalized chitosan were performed by Tran Ngoc Quyen, et al. [47]. In this article the authors reported the preparation and stabilization of colloidal silver nanoparticle solution, with the assistance of chitosan dihydroxyphenyl acetamide (CDHPA), or oligochitosan dihydroxyphenyl acetamide (OCDHPA). The structure of the chitosan derivatives were characterized by ^{1}H-NMR spectroscopy. The morphology of the synthesized silver core-chitosan shell nanoparticles were observed by TEM and XRD techniques, and showed a well-defined core-shell structure of polymer-coated silver nanoparticles (AgNPs). The core-shell NPs exhibited a strong antibacterial activity against *E. coli* and *S. aureus*, at a very low concentration of AgNPs (2.5 ppm).

Silver choloride nanoparticles as an antibacterial agent were investigated by Nguyen Thi Thanh Binh, et al. [48]. In this work silver chloride nanoparticles were prepared by the precipitation reaction between silver nitrate and sodium chloride in an aqueous solution containing poly(vinyl alcohol) as a stabilizing agent. Different characteristics of the nanoparticles in suspension and in lyophilized powder such as size, morphology, chemical nature, interaction with stabilizing agent and photo-stability were investigated. Biological tests showed that the obtained silver chloride nanoparticles displayed antibacterial activities against *Escherichia coli* and *Staphylococcus aureus*.

In Ref. [49] Duong Thi Thuy, Ha Phuong Thu, et al. examined the growth inhibition effect of engineered silver nanoparticles against bloom forming

cyanobacterial *M. aeruginosa* strain. AgNPs were synthesized by a chemical reduction method at room temperature and UV-Vis spectroscopy, SEM, TEM showed that they presented a maximum absorption at 410 nm and size range between 10 and 18 nm. *M. aeruginosa* cells exposed during 10 d to AgNPs to a range of concentrations from 0 to 1 mg l^{-1}. The changes in cell density and morphology were used to measure the responses of the *M. aeruginosa* to AgNPs. The control and treatment units had a significant difference in terms of cell density and growth inhibition ($p < 0.05$). Increasing the concentration of AgNPs, a reduction of the cell growths in all treatment was observed. The inhibition efficiency was reached 98.7% at higher concentration of AgNPs nanoparticles. The term half maximal effective concentration (EC_{50}) based on the cell growth measured by absorbance at 680 nm (A680) was 0.0075 mg l^{-1}. The inhibition efficiency was 98.7% at high concentration of AgNPs (1 mg l^{-1}). Image of SEM and TEM reflected a shrunk and damaged cell wall indicating toxicity of silver nanoparticles toward *M. aeruginosa*.

Microwave-assisted synthesis of chitosan/polyvinyl alcohol silver nanoparticles gel for wound dressing applications was performed by Tran Ngoc Quyen, Nguyen Dai Hai, et al. [50]. The purpose of this study was to fabricate chitosan/poly(vinylalcohol)/Ag nanoparticles(CPA) gels with microwave-assistance for skin applications. Microwave irradiation was employed to reduce silver ions to silver nanoparticles and to crosslink chitosan (CS) with polyvinyl alcohol (PVA). The presence of silver nanoparticles in CPA gels matrix was examined using UV-Vis spectroscopy, TEM and XRD. The interaction of CS and PVA was analysed by FTIR. The release of silver ions was determined by atomic absorption spectrometry. The antimicrobial properties of CPA gels against *P. aeruginosa* and *S. aureus* were investigated using agar diffusion method. Finally, the biocompatibility and woundhealing ability of the gels were studied using fibroblast cells (*in vitro*) and mice models (*in vivo*). In conclusion, the results showed that CPA gels were successfully fabricated using microwave irradiation method. These gels can be applied to heal an open wound thanks to their antibacterial activity and biocompatibility.

Role of collagen concentration in stability of star-shaped silver@goal nanoparticles was investigated by Nguyen Dai Hai, et al. [51]. In this work star-shaped silver@gold (Ag@Au) nanoparticles were synthesized in collagen (Coll) suspensions by a seeding growth approach. The silver nanoparticles were used as seeds for Au development. Coll was used as a protecting agent and the effect of its concentration on stability was also examined. Obtained nanoparticles were then characterized by UV-Vis, TEM, XRD and FTIR. The result was confirmed by the maximum surface plasmon resonance peak at 566-580 nm for each sample indicating the formation of branched Ag@Au@Coll NPs. The average diameters of the branched Ag@Au@Coll NPs were revealed to be 30-50 nm depending on the corresponding component ratio and the pH value. It is interesting to note that the concentration of Coll plays a critical role in the stability of the star-shaped gold nanoparticles. The results offer an understanding of the handling of the electronic and the silver@gold based nanoparticles stability properties.

Conclusion and Discussion

Basic research on nanomedicine in Vietnam began about 5 years ago with the first publications in the year 2012 [1,16]. Since that time it rapidly developed and obtained promising results in following areas of nanomedicine:

- Biomedical utilization of PLA-TPGS and PLA-PEG;

- Dendrimer-based anticancer drug;

- Various utilizations of nanocurcumin in nanomedicine;

- Biomedical application of hydrogel nanocomposite;

- Biosensors and biosensing methods;

- Toxicity and antibacterial activity of different types of nanoparticles.

Results of the research on nanocurcumin were efficiently applied to the industrial production of several food supplements such as CURMAGOLD, CURMIN Nano 22^{+}, HEPOSAL B, FGC and CUMARKUL.

Further development of the basic research on nanomedicine could be directed toward two topics:

- Enrichment of the scientific contents of the basic research works;

- Implementations of the results of basic research both to the diagnosis as well as to the treatment of the diseases.

The development of nanomedicine in Vietnam requires a very large fund, a difficulty of Vietnamese science. However, this difficulty certainly will be avoided by both the great attention of the Vietnamese Government to the plubic health and the friendly financial support of the international community.

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