

Role of Nanofluids in Drug Delivery and Biomedical Technology: Methods and Applications

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Abstract: Recently, suspensions of several nanoparticles or nanocomposites have attained a vast field of application in biomedical research works in some specified conditions and clinical trials. These valuable suspensions, which allow the nanoparticles to disperse and act in homogenous and stable media, are named as nanofluids. Several studies have introduced the advantages of nanofluids in biomedical approaches in different fields. Few review articles have been reported for presenting an overview of the wide biomedical applications of nanofluids, such as diagnosis and therapy. The review is focused on nanosuspensions, as the nanofluids with solid particles. Major applications are focused on nanosuspension, which is the main type of nanofluids. So, concise content about major biomedical applications of nanofluids in drug delivery systems, imaging, and antibacterial activities is presented in this paper. For example, applying magnetic nanofluid systems is an important route for targeted drug delivery, hyperthermia, and differential diagnosis. Also, nanofluids could be used as a potential antibacterial agent to overcome antibiotic resistance. This study could be useful for presenting the novel and applicable methods for success in current medical practice.

Keywords: biomedical applications, nanofluid, diagnosis, therapy, drug delivery, antibiotic resistance

Introduction

Nanofluids are emulsions or suspensions of nanoparticles (NPs) in fluids, which could be used for straight heat transfer enhancement in many industrial applications, heat exchangers, transportation, electronics as well as biomedicine and food industry.¹ There is an increasing interest in the use of nanofluids in nano biomedical technology; hence, their physicochemical properties undergo many changes in comparison with their solid forms. Recently, biological applications of nanofluids have been considered for several usages, such as drug delivery and antibacterial therapeutics.² Also, many papers have been reported about combination systems using nanofluids, imaging and diagnosis, (eg drug delivery +imaging, high fever + imaging), or multimodal imaging (eg optical + MR imaging, PET + MR imaging).³ For the best and safe application of nanofluids, several key requirements have to be satisfied. These necessities are a good characterization of composition, size, crystallinity, and morphology. Besides, stability, non-agglomeration, and biocompatibility are essential properties.⁴ A great portion of the NPs disperses partially in water-based solutions. The dispersion stability mostly relies on the composition, structure, size, and morphology of the NPs.⁵ To attain a stable nanofluid, several procedures may be taken into consideration, which includes nanomaterial synthesis, physical

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stirring, ultrasonic homogenization, surface engineering, and using surfactant and other chemical additives.⁵ Also, the medical safety and legislation approval of these additives must be regarded. Most of the studies about nanofluids have been carried out on the material, surface science, and colloid theory. Hence, many properties of nano-based systems have been optimized. Although, the biomedical applications of nanofluids are far from simple in practice, and require further inspection.^{6–8}

There are rare review articles regarding an exclusive consideration of the biomedical application of nanofluids. There are some papers which generally reviewed the vast uses of nanofluids in a broad range of fields. One of the areas, which is mentioned in such reviews, is the biomedical applications, in a concise and general form. Wong et al⁹ briefly mentioned some of the research works related to each subcategory of diverse applications of nanofluids. Wei et al¹⁰ only indicated the antibacterial activity, and drug delivery. Some authors have contented some paragraphs on the medical applications of nanofluids.¹¹ Also, one could find another review paper, which did not describe the biomedical applications.¹² According to the nanofluid definition, which was mentioned above, all of the nanoparticle-contained suspensions or nanosuspensions were considered, and the applications of such fluids in drug delivery and antibacterial and biomedical treatment are reviewed in this paper. In this review, the methods and applications of nanofluids in a diverse biomedical field are surveyed comprehensively.

Applications in Drug Delivery

The main purpose of the design of a drug delivery system is to release the drug in a controlled manner at the desired site. First studies in drug delivery systems were about drug release kinetics, pH and temperature sensitivity, polymers, nasal delivery, and oral drug delivery.¹³ The use of nanomaterial in drug delivery systems is one of the topics, which has been considered by many researchers in recent years to provide some benefits like being suitable for accurate delivery to the target cells, increased therapeutic properties and safety, decreased toxicity, and biocompatibility.¹⁴ Regarding the development of a nanofluid formulation for drug delivery, the system must afford drug loading and release characteristics, prolonged shelf life, and biocompatibility.¹⁵ One of the most important matters with nanofluidic drugs is the charge of NPs in the fluid. The surface charge of fundamental biological particles in blood is almost negative, and the inner

walls of blood vessels are negatively charged. Thus, they repulse each other, and blood cells do not agglomerate in the vessels.¹⁶ Therefore, commonly, the therapeutic particles must be negatively charged to prevent aggregation.

Opsonization, the process by the opsonin proteins, is a pivotal mechanism that helps macrophages in defending against foreign particles such as bacteria and viruses. In the case of nano-drug delivery carriers, a reduction in the bioavailability of nano-colloidal drugs would be a problem.¹⁷ Considerable efforts have been devoted to dealing with these limitations, and several solutions have been presented. Polyethylene glycol (PEG) adsorption to nanoparticle is the most used method.¹⁷ Negatively charged albumin is another molecule that protects the NPs from opsonization.¹⁸ Several colloidal drug delivery systems (CDDS) of analgesic drugs have shown admissible efficacy in the preclinical and clinical studies.^{19,20}

Magnetic Drug Delivery

Among different types of NPs, magnetic NPs have been noticed widely, as drug carriers. This issue is due to the controllability of these NPs, their small size, and surface property, which allow the carrier to be directed to the desired location via a magnetic field. In magnetic drug delivery, blood acts as the main fluid, while the magnetic NPs act as carriers of the drug. The drug-loaded magnetic NPs would be injected near the tumor, due to the intense and concentrated magnetic gradient; the tumor could absorb the drug. By using this method, the side effects of chemotherapy are reduced. Another advantage of this method is to use higher doses of anticancer drugs, without damaging the healthy side tissues.^{21–23}

One of the most effective ways to treat cancer is the usage of magnetic NPs, placing a magnet near the tumor, and then injecting the drug into the closest vessels to the tumor site. The dynamics of these NPs may be influenced by the peristaltic motion of the waves, which are generated in the cone-shaped asymmetric channel walls. An analysis of the nanofluid flow, influenced by this type of movement, can greatly help the treatment of cancerous tissues.²² Superparamagnetic iron oxide NPs (SPIOs) is the most used magnetic nanoparticle for magnetic drug delivery in the clinical applications. New studies have discussed wide applications of SPIOs in cancer detection, screening, and treatment.^{24,25} Also, a study was done about green biosynthesis of superparamagnetic magnetite Fe_3O_4 NPs and their biomedical applications in targeted anticancer drug delivery

system. Also, some examples of Fe_3O_4 -based NPs, as an anticancer drug vehicle in treating different kinds of cancer cell lines using various anticancer drugs, have been reported in these recent years.²⁶ Besides, in 2018, the enhanced photodynamic anticancer activities of multifunctional magnetic NPs (Fe_3O_4), conjugated with chlorin e6 and folic acid, in prostate and breast cancer cells were reported in a new investigation.²⁷ The SPIOs are made of an iron oxide core and a shell with hydrophilic groups for facilitating solubility. Commonly, the shell could be a fatty acid, organic polymer, or a polysaccharide.²⁸ In a study by Pattayil and Kunnoth²⁹ in 2015, the drug (curcumin) was inserted into a modified cyclodextrin β cavity. Curcumin is one of the well-known medicines for treating cancer, and because of its low ability to dissolve in water, it is necessary to use a carrier to deliver it to the target tissue. The cyclodextrin β is a modified carrier suitable for hydrophilic drugs.³⁰ In an interesting therapeutic dose study, Lim et al³¹ developed the pH-sensitive drug-delivering magnetic NPs (DMNPs) as theragnostic nanocarriers, which release doxorubicin (DOX) under the acidic conditions within cancer cells. They reported that the drug release kinetics of the DMNPs, combined with the NP accumulation pattern in the tumor cells, could be monitored by magnetic resonance imaging (MRI) to guide decisions regarding the optimization of drug dosing schedules. So, the reports of these valuable studies could be used to improve the efficacy of drugs

and reduce their side effects in the smart drug delivery systems.³²

Use of Microelectromechanical Bio-Systems

Regarding the application of microfluidic technology, researchers investigated how to transfer and control the flow. Microfluidic equipment generally has some components such as reservoirs, canals, pumps, valves, mixers, activators, filters, or heat exchangers for delivery with high precision. One of the applications of nano-drug delivery systems is to monitor the target cells' responses to drug stimuli or to facilitate the drug development process.^{9,14,33-37} In this case, the NPs are in an aqueous solution, in which, the concentration of the particles and the solvent temperature are predetermined. As shown in Figure 1, these nanofluids are delivered to the living cells through the micro-channels. Among other applications of this microfluidic device, one can refer to the testing of pharmaceuticals and performing high-efficiency biomedical analyses.^{9,33-36} In Figure 1, there is a reservoir for storing the solution or cleaning fluid. The micro-channels could change the amount of fluid entering the test site by adjusting their resistance or internal pressure.

The main goal is to achieve a uniform concentration of nanomedicine at the micro-channel output. The presence of appropriate heat flux from the lower microchannel wall ensures that the drug-fluid mixture is delivered to the live cells at an optimum temperature (37°C). The amount of this heat flux is a function of the nanofluid velocity and the

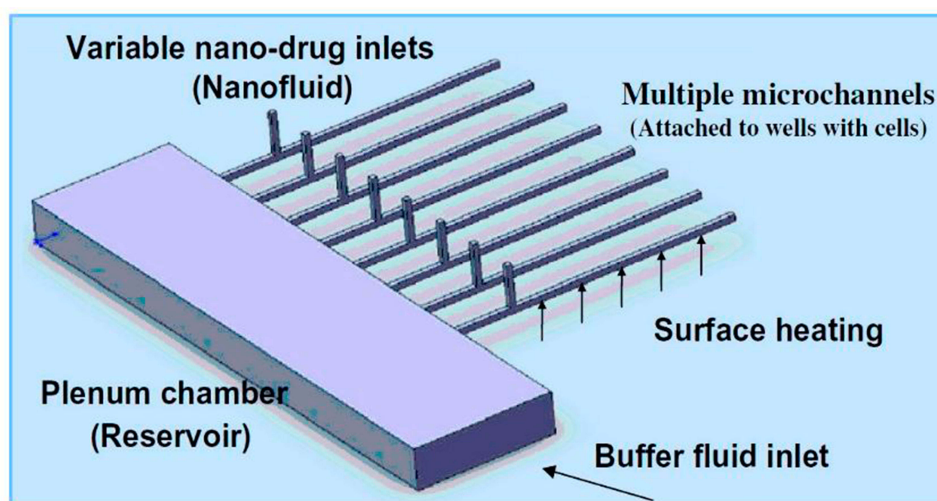


Figure 1 Nano delivery system with eight micro-channels

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velocity of the cleaning fluid. The presence of this heat flux has also a positive effect on the drug's concentration uniformity.³⁸ In general, the concentration uniformity of the nano-drug is affected by some factors like the channel length, the NPs size, and the Reynolds number corresponding to the source of the nanofluid and the main microchannels.³⁸

Nanocrystals and Nanoparticles

Nanocrystals are carrier-free drug NPs without any other jointed molecules. A nanocrystal nanofluid is a suspension of the poorly soluble drug (in most cases) in water, or another solvent stabilized with a surfactant or a stabilizer. The nanocrystal pharmaceutical products are available in the market; Rapamycin, Aprepitant, Fenofibrate, and Megestrol are some of the nanocrystal drugs. The main advantages of nanocrystals are their solubility enhancement, increased dissolution velocity, saturation solubility, user-friendliness, and high bioavailability.³⁹ ZnO NPs and their combinations are the best in the nanobiotechnology and nanomedicine applications. The reason for this issue is the proper condition of electrons in the valence-shell of the NPs (with large bundles).⁴⁰ The ZnO NPs, because of their biological properties (anti-bacterial, low toxicity, UV blocking), could be used in cancer treatment such as breast cancer.⁴⁰ In some of the studies,⁴¹ the cytotoxic effects of zinc oxide NPs in hepatoma cells have been investigated. It was also shown in,^{41–43} that ZnO caused further damage to the rapid process of dividing cancerous cells.

In a study by Abdolmohammadi et al⁴² in 2017, the cytotoxic effects of two types of ZnO nanomaterials on the growth of MCF-7 cell lineage in breast cancer were investigated. The results of this study showed that, with increasing the concentrations of ZnO NPs in 48 and 72 hours of treatment, the survival rate of MCF-7 cell lines in breast cancer decreased. Dotan et al⁴⁴ developed a nanofluid platform by conjugating multi-walled carbon nanotubes (CNTs) with either thyroid-specific antibody or thyroid-stimulating hormone. The nanofluid selectively targeted and killed the papillary thyroid cancer cells in vitro with minimal cytotoxic effect on the non-targeted cells.

Applications in Treatment Hyperthermia Method

Hyperthermia is a method for treating cancer. The term hyperthermia is derived from the two Greek words, "hyper" and "thermia", which mean rise and heat,

respectively.⁴⁵ The studies show that heating in the temperature range of 41 to 46 °C, for at least 20 to 60 minutes, stops the cancer cells' growth.^{46,47} The hyperthermia method has some shortcomings like the heterogeneous distribution of temperature in the tumor mass and the inability to prevent overheating in deep-tissue tumors. Therefore, for responding to the need for an appropriate solution to overcome these problems, scientists have suggested magnetic NPs. With the help of magnetic NPs, the heat could be provided uniformly by this method, which is called as the MNFHT (magnetic nanofluid hyperthermia therapy). Also, the control of heat distribution and temperature is essential in this therapeutic approach.^{48,49}

To express the distribution of energy, the SAR (Specific Absorption Rate) has been used, whose unit is W/m^3 or W/g .³⁵ This number indicates the power of magnetic NPs to eliminate cancerous cells, which is measured by numerous temperature sensors placed in the agarose gel. In a study by Salloum et al⁴⁹ in 2007, nanofluids were injected into an agarose gel to study its movement in extracellular tissue. This research was carried out as in vitro, and agarose gel was used as a tissue-equivalent.⁵⁰ The purpose of this study was to provide a method for controlled tumor heating; it was shown that, if the nanofluid distribution within the gel was spherical, this goal could be achieved. In tumors with unusual geometry, the multiple injection method has been proposed to achieve a uniform increase in the tumor temperature.⁴⁹ According to the studies, the cubic geometry of NPs has more SAR than the other forms (spherical, rod, star, polyhedron, and cone).⁵⁰

The SAR values are influenced by some factors such as the size and shape of the NPs, temperature, frequency of the magnetic field change, and the intensity of the magnetic field.^{46,50} One of the important factors in determining the efficiency of magnetic NPs, is their size. The small size of NPs has some advantages, including ultra-paramagnetic (ultra-magnetic) states of NPs, better dispersion, better heat distribution, prevention of agglomeration, and an increase of SAR. Despite these advantages, if the NP size is less than usual (2–5 nm), their performance would be reduced.⁵⁰ In 2005, researchers reported that superparamagnetic NPs (10 to 40 nm in size) were suitable for clinical applications, due to generating significant heat and low-frequency variation.⁵¹

Magnetic Fluid Hyperthermia

Magnetic fluid hyperthermia is the selective exposure of heat to the desired tissue using magnetic NPs in the presence of an

external magnetic field.⁵² In a study, conducted by Salloum et al⁵³ on experimental lab mice in 2008, the rate of temperature increase in animal tissues during hyperthermia was investigated, by using magnetic NPs. In this research, two critical parameters in magnetic hyperthermia were mentioned, one was the rate of blood perfusion, and the other one was the amount of nanofluid, which was delivered to the tissue.⁵³ Carbon nanotubes (CNTs) could be used under the influence of the magnetic field, to treat cancer cells. In the related research works, NPs are injected into the blood vessels near the tumor, and a magnet is placed near the tumor.^{54,55} A controlled drug delivery system has been developed, with doxorubicin-loaded magnetic PLGA, poly(lactic-co-glycolic acid), microsphere, for inhibition of tumor growth in breast cancer⁵⁶(Figure 2).

Nano-Cryosurgery

The cryosurgery method is one of the most effective ways for complete treatment and control of tumor cells. In this method, liquid nitrogen or solid carbon dioxide is used. Creating an

extremely cold condition causes the formation of ice crystals, and thus, the membrane of the desired cell could be broken due to a decrease in the amount of liquid water (dehydration).^{36,57} However, the use of this method has some problems such as inappropriate freezing, which may damage the healthy side tissues. The tumor tissue is loaded using highly-conductive NPs to improve the freezing capacity.^{35,36,57} Some researchers have investigated the toxicity of NPs and their effects on healthy tissues. By these investigations, they have found that Al₂O₃, Fe₃O₄, and Au NPs are biologically suitable, which could be widely used in medical applications.^{29,30,37,38} It has also been shown that Au NPs have the highest freezing efficiency among all types of utilized NPs, which produce a maximum ice-ball size. Besides increasing the freezing rate, the presence of NPs could also control the size and growth of ice crystals, which are formed during the freezing process. This property causes the destruction of undesired malignant tissues with minimum harm to the surrounding healthy tissues.³⁶ The variation in kinds and dosages of NP solutions could play diverse roles in the freezing process and

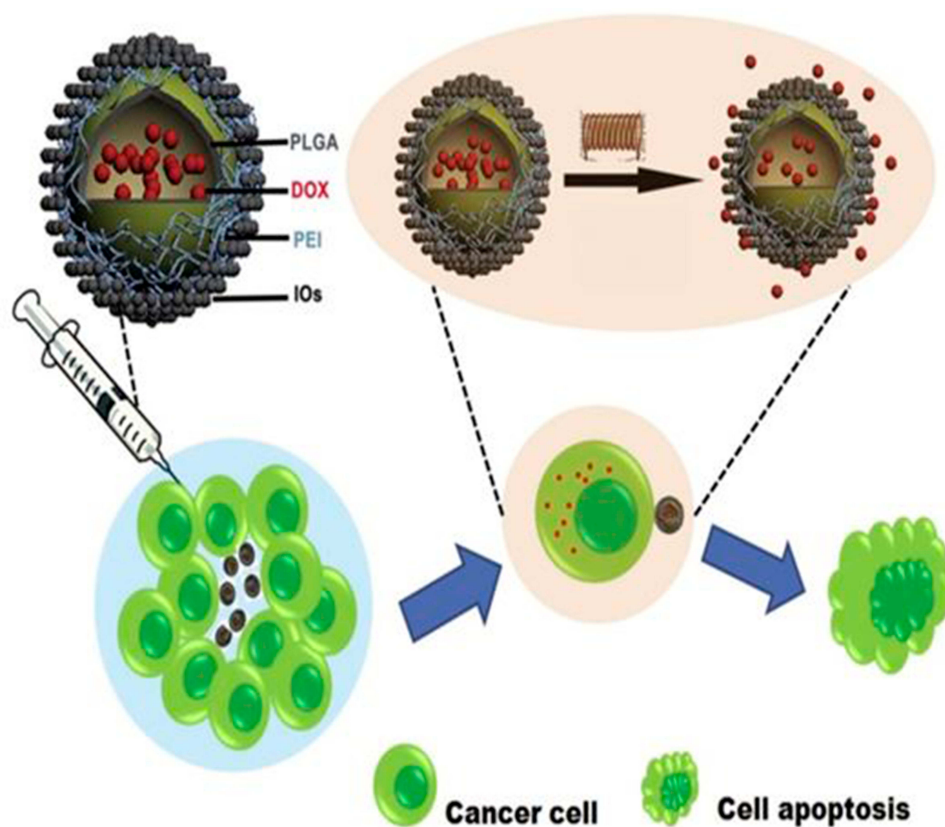


Figure 2 Depiction of magnetic PLGA hollow microsphere response in altering the magnetic field.

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lead to different freezing efficacy. Therefore, the selection of NPs and optimization of the NP suspension dose would be important issues for future research works.⁵⁸

Magnetic Nanofluids for Anemia Treatment

One of the preconditions for using magnetic iron oxide NPs in medical applications is their stability in the fluid interface.⁴³ In the research work of Vazhnichaya et al⁵⁹ in 2015, they obtained a nanofluid containing sustained magnetic NPs, which had anti-anemic properties. The stabilization of these NPs was accomplished by using PVP (polyvinyl pyrrolidone) and Mexidol (2-ethyl-6-methyl-3-hydroxy pyridine succinate). Then, they tested the material on experimental animals (109 male albino mice) in both reasonable conditions, after severe blood loss. The results of this study indicated that the nanofluid stimulated the production of red blood cells (RBCs), both hemoglobin and hematocrit, in healthy animals. When severe anemia occurs due to a blood loss, a nanofluid helps to recover this loss and increase the number of reticulocytes. This nanofluid stimulates erythropoiesis in the intact animals and activates the regenerative reaction of erythron in anemia, due to blood loss.

Radiofrequency Ablation

The Radio Frequency Ablation (RFA) is a medical approach, in which the radio waves of short wavelengths (350 to 500 kHz) generate much heat in the desired tissue. In fact, in this method, an ablation electrode enters the

tissue of the tumor, then the temperature increases because of the waves generated by the electrodes. The surrounding tissue, usually the tumor tissue, would be heated then, which leads to tissue destruction. If the given heat were sufficient enough, the tumor tissue would disappear within a few minutes.^{60,61} In a study by Wu et al,⁶¹ the application of iron NPs (iron NPs with carbon coating) was investigated by the RFA method. The results of the research showed that the use of nanofluid led to a 41% increase in thermal conductivity.⁶¹

Applications in Diagnosis Imaging

One of the most interesting applications of nanomaterials in diagnostic medicine is their usage in magnetic resonance imaging (MRI). The use of magnetic NPs enhances the contrast and sensitivity in MRI (Figure 3). Super-paramagnetic NPs (SPMNP) is one of the best choices for promoting contrast in MRI. These agents could consist of iron oxides, gold, and gadolinium NPs.⁶² The SPMNP is composed of an iron oxide core and a polymeric matrix, which provide colloidal stability; the core could also contain Fe/Mn composite. Several injectable magnetic contrast agents have been proved by the US Food and Drug Administration (FDA) and the European Medicines Agency (EMA). Gadolinium-based contrast agents are frequently used in MRI.⁶³ Due to the gadolinium toxicity concerns, especially in patients with renal failure, its application confronts some limitations.⁶²

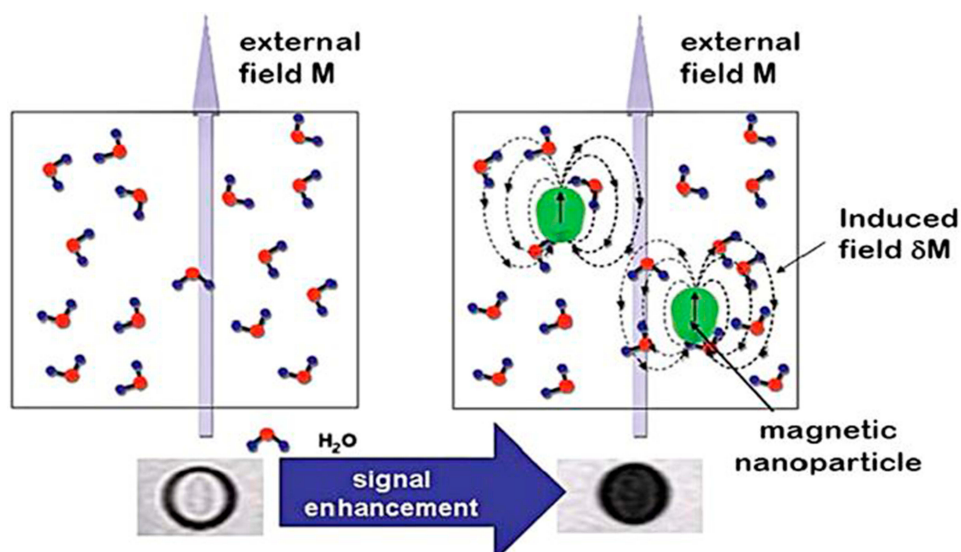


Figure 3 Magnetic contrast effect of magnetic nanoparticles in water, magnetic field results in darker magnetic resonance image.

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The MRI contrast agents, from the outlook of application, could be classified into three groups: the extracellular fluids (known as the intravenous contrast agents), the intravascular contrast agents (known as the blood pool agents), and the target-specific agents. Some of the MRI contrast agents are administered orally, and some formulations have been developed for intravenous injection.^{62,64} The safety and tolerance of the contrast media are important considerable factors. A good contrast agent must be biologically and chemically inert and fully eliminated from the body without any side effect and adverse reaction.^{64,65} Many of such contrast agents are available in the market, which is used consistently.^{66,67}

The targeting of contrast agents leads to a high accumulation of agents at the target sites. By the targeted MRI, a high accumulation of contrast agents in the desired site leads to a specific diagnosis. The targeting agents usually attach to the tissue-specific antibodies on the target organ. Most of the target-specific contrast media have been exploited for liver imaging.⁶⁸ Superparamagnetic iron oxide and liposome-based targeting contrast agents are commercially available.⁶⁹ In this regard, Fe₃O₄O-dextran NPs (Fe₃O₄ with oxidized dextran coating) have been used to create contrast in MRI imaging. These NPs have important properties such as good stability, biocompatibility, bioconjugation, and low cytotoxicity.⁷⁰ Huang et al⁷¹ showed the MRI images of cancer cells, which were added to Fe₃O₄O-dextran NPs (with antibody titers), at various concentrations. With an increase in the iron concentrations from 0.75 mM to 1.15 mM, the image of cancer cells was darker, indicating that the presence of NPs increased the contrast of MRI. Also, with an increase in the size of the nanoparticle core, at a constant concentration, the images were darkened from NP5 to NP15. The images were taken in two modes, with and without antibodies. These nanofluids are also suitable for their usage in drug delivery applications, magnetic hyperthermia, and high-efficiency magnetic bio-separation.

Antibacterial Applications

As a result of excessive use of the common antibacterial chemicals, resistant strains of pathogens emerge day by day. Hence, the development of new solutions toward the control of resistant pathogens seems to be necessary. Over the last few years, several organic and inorganic nanoparticle suspensions have shown antibacterial properties.⁷²

Metal and Metal Oxide Nanofluids

Antibacterial agents play an essential role in the industry, including the disinfection of water, textile industries, medical applications, and food packaging.^{73–75} Among the various types of metal oxide NPs, zinc oxide (ZnO) has a significant ability to prevent bacterial growth in a wide range of bacteria.^{75,76} The antibacterial activity of ZnO nanofluids which are safe to human cells has mostly been studied among other nanofluids.⁷⁷ Based on the morphological studies on the bacterial cell wall, treated with ZnO NPs, by SEM and FESEM, several aspects of ZnO toxicity have been revealed (these NPs cause damage to the bacterial cell wall). The creation of reactive oxygen species (ROS), and the release of antibacterial ions, mainly Zn²⁺, are other aspects of the ZnO toxicity.⁷⁸ Using dispersants such as polyethylene glycol (PEG), defloculants comprising sodium silicate, or sodium carbonate has improved the stability of ZnO nanofluids.^{78,79}

Also, TiO₂ and SiO₂ NPs have similar antibacterial properties with ZnO₂. However, the antibacterial properties of ZnO are higher than that of TiO₂ and SiO₂.⁷⁵ Illumination with UV light leads to the production of reactive oxygen species (ROS) and more antibacterial effect. These three NPs are photosensitive, while TiO₂ has been utilized in water disinfection systems.⁸⁰ Also, MgO and Mg(OH)₂ nanomaterials have attracted much attention over the years, due to their applications in the field of pharmaceuticals.⁸¹ It has been reported that Mg(OH)₂ nanomaterials have a significant antibacterial effect on *E. coli*, *B. phytofirmans*, and some other bacteria.⁸² Dong et al⁸² stated that the antibacterial mechanism of Mg(OH)₂ NPs would be very different from those of metal-based compounds; accumulation of OH⁻ ions in bacterial cells increases the pH level to 10, which results in the death of bacteria. Also, MgO nanoparticle is an effective bactericidal agent against the foodborne pathogens including *E. coli* and *Salmonella Stanley*.⁸³ Lueng et al⁸⁴ reported that the MgO nanofluid toxicity towards *E. coli* could occur in the absence of ROS production and oxidative stress. Therefore, they proposed a new theory on the MgO toxicity mechanism, comprising the damage of the cell membrane without lipid peroxidation.

The antibacterial activities of Cu and CuO NPs have been proved against a spectrum of gram-positive and gram-negative bacteria.^{85–88} The antibacterial activity depends on the size of NPs and the synthesis temperature of the nanoparticle. The smaller CuO NPs, the more antibacterial activity is achieved. The CuO NPs can path through the bacterial

cell wall.⁸⁸ It is imagined that these NPs bind to the cellular enzymes and block the vital activities of the cell.^{86,89} The CuO NPs have no significant cytotoxicity on the HeLa cell lines.⁸⁶ Thus, it seems that CuO NPs cannot enter eukaryotic cells via the cytoplasmic membrane.

Silver and its compounds have been used for centuries for healing wounds and scalds, and disinfection of water. By the development of a new generation of antibiotics, the use of silver-based compounds has been limited. The advent of nanotechnology in recent decades has attracted new attention to the antibacterial use of nano-sized silver.⁹⁰ Due to the cytotoxicity and environmental toxicity of silver nanomaterial, and its possible adverse effects, extensive research works have been conducted on the silver toxicity. Silver NPs have a broad range of toxicity mechanisms, mainly the perturbation in mitochondrial function by altering mitochondrial membrane permeability. Moreover, silver NPs induce inflammatory responses due to the production of ROS.⁹¹ Because of the broad range of toxicity mechanisms of silver, the emergence of resistant strains seems to be implausible.⁹² In addition, gold NPs have been recognized as a biocompatible and relatively

less cytotoxic nanomaterial with versatile applications. The antibacterial activity of gold NPs is not related to the production of ROS. According to Cui et al,⁹³ the antibacterial activity of gold NPs is generally based on two mechanisms: inhibition of ATP synthesis by altering membrane potential and inhibition of tRNA binding to the ribosome.

According to the above explanations, in biomedical application, it should be borne in mind that metallic NPs have few shortcomings like biocompatibility issues, stability, and proper excretion from the body. For metal and metallic oxide NPs, the solubility problems are also important. The release of metal ions of dissolved NPs, has a relation with the toxicity that been observed. The biological characteristics of NPs have significant correlations with their nature and structures. Therefore, consideration of the changes in them such as surface modification and artificial control of size and shape, reduce their toxicity, and improve their biocompatibility.

Composite Nanoparticles

In other studies, to produce a combined magnetic nanoparticle with improved colloidal stability and appropriate

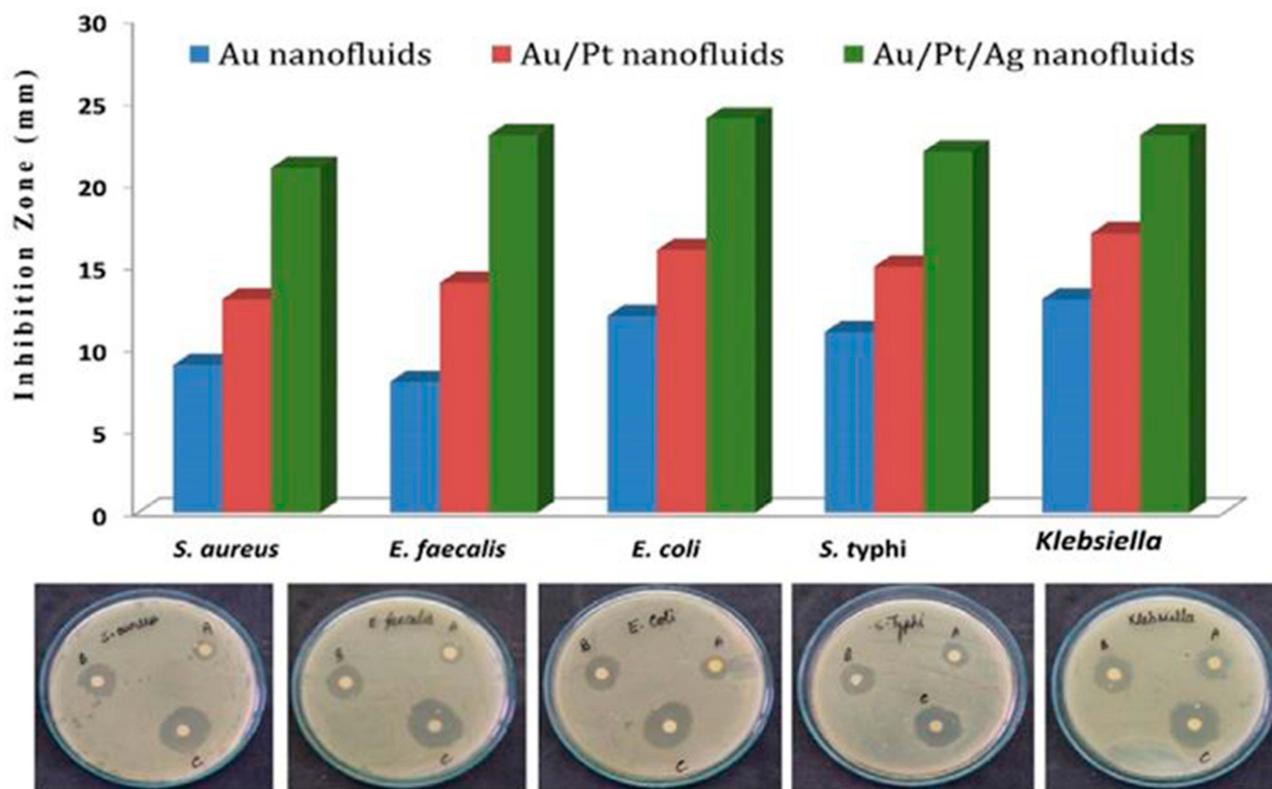


Figure 4 The results of trimetallic Au/Pt/Ag-based nanofluid treatment for an enhanced antibacterial response; "A," "B" and "C" in the agar plates correspond to Au, Au/Pt and Au/Pt/Ag nanofluid, respectively.

Note: Reprinted from Materials Chemistry and Physics, 218, Yadav N, Jaiswal AK, Dey KK, et al., Trimetallic Au/Pt/Ag based nanofluid for enhanced antibacterial response, 10–17, Copyright (2018), with permission from Elsevier.⁹⁶

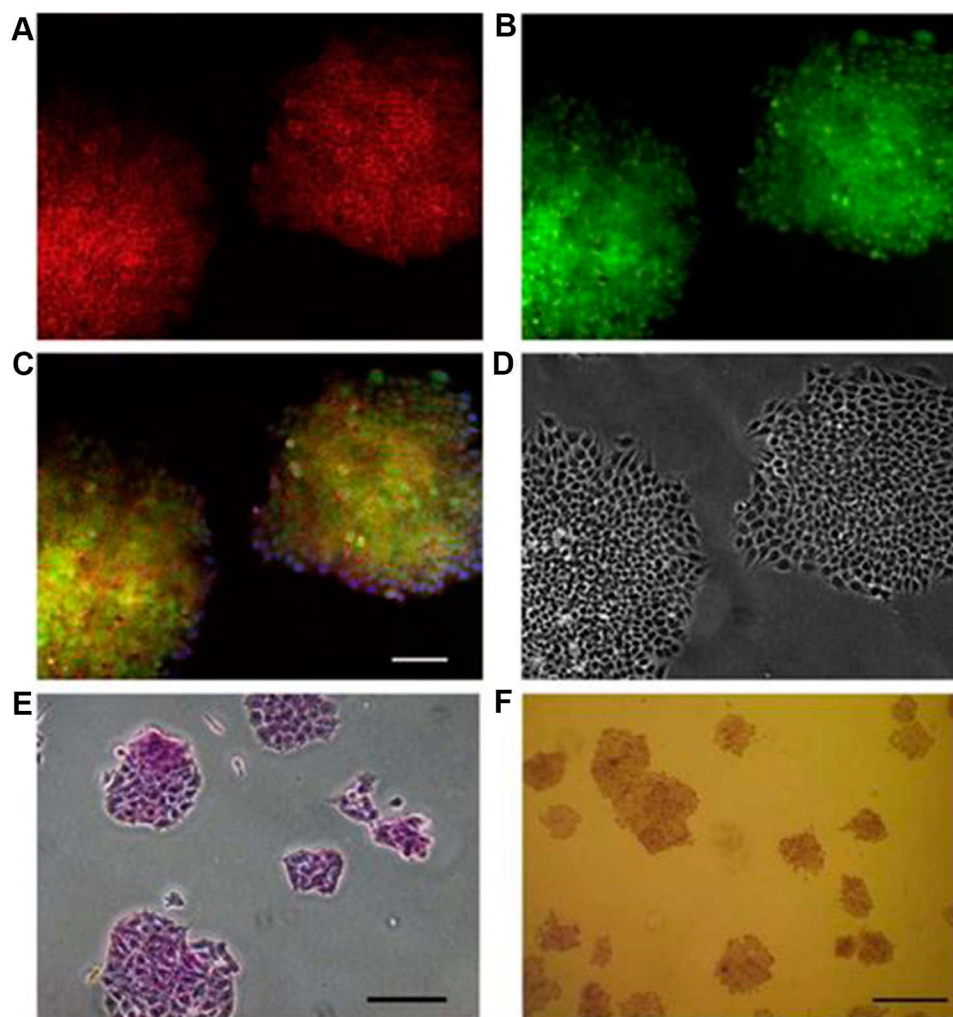


Figure 5 Fluorescence micrographs display high levels of staining for the surface glycoprotein SSEA-1 (**A**) and Oct-4 transcriptional activity, as denoted by GFP expression (**B**). (**C**) The merged view of the red and green channels indicates extensive co-expression of the two markers and DAPI nuclei staining (blue). Phase-contrast image shows cells with a high nuclei/cytoplasm ratio and compact colony formation typical of pluripotent ES cells (**D**). Histochemical staining shows the strong expression for alkaline phosphatase at 10× magnification (**E**), which was seen to be well distributed within each colony as observed at a lower 4× magnification (**F**). **Note:** Reprinted from Cryobiology, 56(3), He X, Park EYH, Fowler A, et al., Vitriification by ultra-fast cooling at a low concentration of cryoprotectants in a quartz micro-capillary: A study using murine embryonic stem cells, 223–232, Copyright (2008), with permission from Elsevier.⁹⁹

antibacterial property, zinc oxide was combined with iron oxide. The anti-bacterial efficiency of these NPs were tested on two types of bacteria; *Staphylococcus aureus* and *Escherichia coli*.^{94,95} The results of these studies indicated that the anti-bacterial properties of this compound were proportional to the weight ratio of [Zn]/[Fe]; so that, when the ratio got higher, the antibacterial property increased.⁹⁵ It was also shown that ZnO particles had the most antibacterial activity against *E. coli*. While the combination of zinc oxide and iron oxide, with a weight ratio of [Zn]/[Fe] greater than 1:1, had a great antibacterial effect on *Staphylococcus aureus*.⁹⁵ In 2018, researchers evaluated the influence of a trimetallic Au/Pt/Ag-based nanofluid on different bacterial strains and showed that

the trimetallic nanofluid had a better effect than both monometallic Au nanofluid and bimetallic Au/Pt nanofluid⁹⁶ (Figure 4).

Also, Fe₃O₄/oleic acid nanofluid has been proposed as a controlled release agent for various compounds.⁹⁷ The role of Fe₃O₄/oleic acid for carrying cephalosporin antibiotics and the antibacterial activity of the nanofluid have been proved on *S. aureus* and *E. coli* cultures.⁸⁷

Other Applications of Nanofluids Nanofluids in Wound Dressing

Arising excessive infections in skin lesions is common during the treatment; therefore, the need for a proper dressing is

much important and necessary. Anghel et al⁹⁸ in 2013, investigated the use of iron nanofluid in wound dressing to prevent the colonization of *Candida albicans* and biofilm formation. The desired nanoparticle was a combination of active magnetic NPs such as iron oxide, and the dressing patches were immersed in this nanofluid. The final result of this study was that the combination of the unique features of iron oxide NPs and *Satureja hortensis* oil could result in providing a new product, which prevented the formation of biofilms and fungi on a variety of medical and clinical equipment surfaces.

Cryopreservation

He et al⁹⁹ developed a quartz micro-capillary system for novel ultra-fast vitrification of mammalian cells. The results of their study indicate that vitrification at a low concentration of intracellular cryoprotectants would be a viable and effective approach for the cryopreservation of murine embryonic stem cells. The traditional vitrification methods usually use very high concentrations of cryoprotectants (commonly more than 4 M), which are often toxic. In this study, the concentration of cryoprotectant was 2M, the same as the concentration which is generally used for the traditional slow-freezing methods. Hence, this protocol had the advantages of the classical slow-freezing methods and fast cooling methods, simultaneously. This method was executed the vitrification of murine embryonic stem (ES) cells with a viability rate similar to the non-frozen control cells. The preservation of undifferentiated properties of the pluripotent murine post-vitrification ES cells was verified by the expression of three different proteins, including transcription factor Oct-4, membrane surface glycoprotein SSEA-1, and alkaline phosphatase. Figure 5 represents the immunofluorescence, and histochemical analysis of the pluripotent ES cells post vitrification.

Conclusion

Among the wide variety of applications of nanofluids, one could point out the usage of these fluids in medical and biomedical cases. In this study, the applications of nanosuspension nanofluids in drug delivery, medical treatment, disease diagnosis, antibacterial cases, wound dressing, and cryopreservation is surveyed. Based on these novel topics, the papers related to the mentioned case were studied and their contents and results were described and analyzed. This study aimed to establish a proper template for these special studies and making easy the future road map in case of the nanofluid applications in biomedical treatment, diagnosis, and antibacterial cases. Based on the conducted

research works, a summary of concluding remarks are listed. Then, some suggestions are recommended for future works.

- In drug delivery, the main aim has been the prevention of aggregation and long-term stability. The reduction in the bioavailability of nano-colloidal drugs has been focused on by many researchers, and many studies have been carried out with this regard. Nanocrystals, CNTs, and gold, ZnO, and magnetic NPs have been used for their special properties. Magnetic nanoparticle-based hyperthermia has been used for heating the tumoral tissue, killing of tumor cells, or making them more sensitive to the effect of anti-cancer drugs and radiation. Nanofluids increase the destruction of tumor tissue via enhancing the thermal conductivity. For drug delivery, specifically for cancer cells, limited types of nanofluids have been tested. So, other types of magnetic nanofluids are recommended for obtaining possible valuable results per each type of disease and cancer.
- Nowadays, the application of nanofluids in targeted MRI, which is the most interesting method in imaging and diagnosis, has been increased significantly. The role of contrast agents is vital in the MRI, where some nanofluids such as Fe₃O₄-based fluids have been considered for this case. Trying other nanofluids could be useful for achieving the optimized contrasting behavior of different agents in different diagnosis cases.
- Photosensitive NPs such as ZnO, TiO₂ and SiO₂ have more antibacterial effect than other NPs; while the gold NPs have been recognized as a biocompatible and relatively less cytotoxic. Regarding the literature review and focus on the conducted research works, the following suggestions are recommended for future works:
 - Finding new applications of nanofluids in biomedical and medical issues.
 - Increasing the in vivo and in vitro testing trials on the nanofluids agents.
 - Testing different types of nanofluids in drug delivery, treatment, diagnosis, and bacterial disinfection.
 - Comparing different contrast agents for the diagnosis methods.

Disclosure

The authors declare that they have no conflicts of interest in this work.

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