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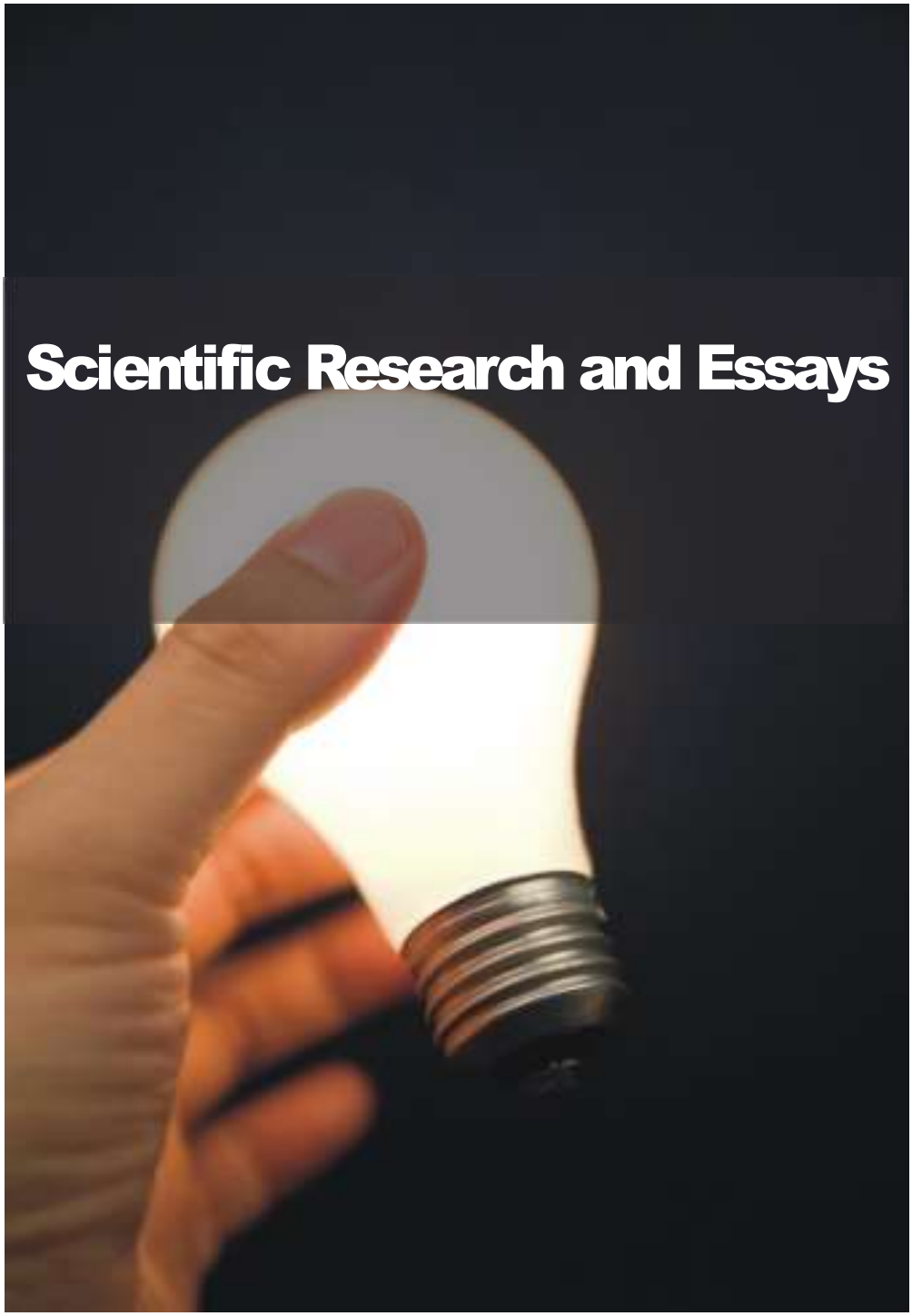

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Review

Nanomedicines: Challenges and perspectives for future nanotechnology in the healthcare system

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A novel approach of combining nanotechnology to the pharmaceutical and biotechnological field resulted in the formation of nanomedicines. Nanomedicines have progressed to a more considerable extent for curing irremediable diseases such as neurological defects, cardiovascular defects, etc., because of its minute size which assists in increased surface area and hence a remarkable dissolution profile. In addition to the health care sector, modernization of nanotechnology has also been implemented in other industries like cosmetics, electronics, catalysis, and chemical industries. Nanoparticles can be made by using polymers, either lipids or inorganic compounds like metals. They can be prepared by using either top to bottom or bottom to top approach. Interestingly, polymeric nanoparticles have provided an enormous opportunity to alter the surface of the nanoparticles leading to better drug delivery and drug targeting. However, these have the potential to induce toxicity as well. Also, the toxicity profile still has to be investigated. Moreover, characterization of the nanomedicines is always trouble, which has created a gap between conventional drugs and nanomedicines.

Key words: Nanomedicines, polymeric nanoparticles, lipid nanoparticle, drug targeting, nanotoxicology.

INTRODUCTION

The term nanomedicine referred to as the application of nanotechnology or nanotools for therapeutic and diagnostic purpose. In the 21st century, nanomedicine appears as an advanced tool of medical science which claims to promote the therapeutic potency of the drugs, reduce the adverse effect, offers patient-friendly

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techniques and overcome the limitations of conventional therapeutic approaches (Aschengrau, 2008; Pautler and Brenner, 2010).

Nanomedicines show immense potential for targeting the drug to its active site making it available for a sustained period. Moreover, it also protects the drug from harsh surroundings and facilitates drug targeting (Ventola, 2012; Wolfram et al., 2015; Bobo et al., 2016; Havel et al., 2016).

The unique physicochemical properties and smaller size of the nanotools attract the researchers and scientist. The smaller size (below 1µm) allows the entry of nanoparticles to the critical areas of the human body like brain, cardiac tissues, tumor cells, etc., improves the drug permeation through biological membranes and thus increases overall bioavailability of the drug (Pautler and Brenner, 2010; Agrawal et al., 2018a). The physiochemical properties related to these nanomedicines play a crucial role in its novelty. The suited surface chemistry with a stable resonating capacity of the nanomaterials helps for the formation of nanomedicines. Furthermore, a tenacious potential and biocompatibility of nanomaterials assist in the development of these nanomedicines (Dvir et al., 2011; Lozano et al., 2012a,b; Escamilla-Rivera et al., 2016). Interestingly, they show a high surface-to-volume ratio which indicates that one can easily modify its surface for better drug loading and targeting (Antimisiaris et al., 2014).

Nanotechnology has played a significant role in pharmacy by reducing the number of raw materials needed and the energy spent on its optimization. However, during their production, a large amount of energy and chemically hazardous solvents are utilized which may harm the body as well as the environment (Han et al., 2012; Khan et al., 2012; Xu et al., 2012; Zhang et al., 2015; Cerrillo et al., 2017).

Although nanomedicines are being formulated to get desired and highly effective diagnostic as well as less toxic treatment, but the main concern here is to assess the safety procedures, which are performed to evaluate the total quality and efficacy of nanomedicines. Essentially, the pharmacokinetic and pharmacodynamic profile of the formulated nanoparticles must be assessed for its toxicity and safety (Brand et al., 2017).

The two most desired properties required for the evaluation of any successful nanomaterial is its efficacy and safety (Ciappellano et al., 2016). Nanomedicines are formulated to achieve specific objectives such as:

1) Solubility enhancement of hydrophobic drugs.
2) Increasing the residence time of drug within the body.
3) Decreasing the side effects of the drug.
4) Monitoring the drug release pattern.

Administering nanomedicine provides two combinations, improvement of disease as well as individual risk they produce. The extent of exposure of these medicines can be characterized to get a toxicity profile associated with that nano-dosage form. The characterization of toxicity can be achieved by performing the in-vitro and in-vivo assay and plotting a dose-response curve (Linkov et al., 2008; Oberdorster, 2010). In this review, the challenges associated with formulation, characterization and drug delivery of nanomedicines have been discussed. The future directions to be followed to make these nanomedicines safe and effective have also been reviewed (Ciappellano et al., 2016).

PREPARATION OF NANOMEDICINES

Nanoparticles, prepared by using a wide variety of materials such as lipids, most importantly liposomes that are made up of phospholipid bilayer covering an aqueous core (containing therapeutically active drug) hence are biocompatible, despite this, are least stable within blood circulation. Numerous category of polymers can also provide a better option for nanoparticle preparations providing a chance to vary the physiochemical properties of nanocarriers, but they also show some toxicity related to solvents used during their preparations. The use of inorganic materials such as metals also called metallic nanoparticles had been made, but unfortunately, these are less popular for therapeutic drug delivery due to the metal toxicity associated with them.

Nanoparticles can be prepared by using top to bottom approach, in which the bulk material remains homogenized, chemically etched or sputtered so that they can attain nanoparticle size range. In contrast, base to top approach includes size expansion from atoms to nuclei than to nanoparticles using sol-gel process, chemical precipitation or by using green synthesis where plant extracts, used as stabilizing and reducing agents (Devatha et al., 2018).

THE RATIONALE BEHIND THE USE OF NANOMEDICINES

Nanoparticles have tremendous potential to increase the bioavailability of the drug by improving its pharmacokinetic and pharmacodynamic profile (Kumar et al., 2017). Their high surface-to-volume ratio attracts the researchers to do several surface modifications like PEGylation, ligand binding, etc. for better drug targeting. Nanoparticles can be administered parentally conveying better drug circulation, drug protection, and a sustained release (Agrawal et al., 2018b). These can also be applied topically, but there may be a chance for dose dumping which can lead to drug toxicity. Active drug targeting, can be achieved by employing ligands such as peptides, antibodies, etc., to the surface of the nanoparticles which upon systemic circulation reach the active site where the ligand will bind to the receptor and engulf the nanoparticle loaded with the drug through

endocytosis (Etheridge et al., 2013; Verma et al., 2015).

PHYSIOCHEMICAL PROPERTIES ASSOCIATED WITH NANOMEDICINES

Nanomaterials must exhibit a particular particle size having an optimized zeta potential essential for its stability. Physiochemical properties associated with nanomedicines include parameters such as particle size, surface morphology, the zeta potential of the nanoparticles. During formulation, it becomes difficult to get precise, and reproducible particle size is failing drug loading or encapsulation (Karnik et al., 2008; Rhee et al., 2011; Chen et al., 2012; Kim et al., 2012; Shi et al., 2017).

Nanomaterials have the potential to exaggerate toxicity due to their different properties in chemical, optical and magnetic areas. Moreover, increased penetration of small-sized nanoparticles within the lungs causes airway blockage leading to alveoli dysfunction (Maynard et al., 2011).

CHARACTERIZATION OF NANOMATERIAL

To get better stability profile, nanomaterials are characterized for various parameters like optical detection, physical properties, and chemical reactivity. When the drug is loaded within any nano-formulation, which evaluates its optical properties, these hinder the light scattering ability of drug. Moreover, due to these nanomaterials, there is decreased emission of fluorescent probes leading to false optical measurement (Dhawan and Sharma, 2010; Dobrovolskaia et al., 2010; Powell et al., 2010; Ciappellano et al., 2016). Consequently, these problems can be solved by just removing the nanomaterial before reading the nanomedicine into the optical analyzer (Ahamed, 2011; Oostingh et al., 2011; Kroll et al., 2012; Costa et al., 2016).

While characterizing the physical properties by assay, these nanomaterials tend to adsorb the molecular probe and thus prevent the catalysis of the end product (Kroll et al., 2009; Wolfram et al., 2015). Metal nanoparticles, like gold and silver nanoparticles, also tend to alter the absorbance and thus to decrease the fluorescence (Oostingh et al., 2011).

BIOMEDICAL APPLICATION OF NANOTECHNOLOGY

Everyone is very much familiar with the standard diagnostic and therapeutic use of nanotechnology as a drug carrier system, diagnostic agents, drug targeting system, etc. Along with this nanotechnology, it also offers excellent opportunity to develop advanced medical devices and smart technologies to treat life-threatening disorders more effectively. In this section, some of the advanced biomedical application of nanotechnologies were highlighted, which could change the conventional way of clinical practices (Abeer, 2012).

Nano regenerative medicine

Another exciting application of nanomedicine is the amalgamation of nanotechnology with stem cell technology to produce regenerative medicines. Stem cells possess an ability to recreate any human tissue and can be used for bone, muscle and organ regeneration. However, the uncontrolled propagation limits its application. Thus, the combination of nanotechnology with stem cell could offer an excellent opportunity to develop promising regenerative medicines. Some nanomaterials like magnetic nanoparticles, fluorescent nanoparticles, etc. along with the stem cell technology can be used for molecular imaging, implants, tissue scaffold, skin grafting and organ replacement (Arora et al., 2012; Alexander et al., 2018).

Nanodevice for diagnosis

Precise diagnosis of pathological condition especially in case of chronic diseases is essential for the proper therapy. Late or improper diagnosis may delay or misguide further treatment especially for CNS disorders, cancer, etc. Thus, a highly sensitive, personalized and real-time diagnosis system is highly desirable. The nanoscale material offers enormous scope to be developed as an advanced diagnostic tool (Hu et al., 2011; Khare et al., 2014). A nanoscale device or nanomaterials could affect directly interaction with the biological system at the subcellular and molecular level and thus can be developed as a more sensitive and accurate molecular probe and biosensors which allow early stage precise diagnosis (Bouck et al., 1996; DeBerardinis et al., 2008).

As biocompatible implants

Despite the conventional implants, which are mostly made of different type of metals like stainless steel for bone, hip and knee replacement, copper implants as intrauterine contraceptive devices, etc., the nanomaterials can serve as biocompatible implants. The nanomaterial-based implants could more closely mimic the cellular behavior and can be easily tuned according to the physiological environment (Abeer, 2012).

In cancer therapy

Real-time diagnosis, target specific treatment and

tracking the effect of therapy has been a significant challenge to treat different types of cancer. Nanomedicines and nanodevices resolve to have the ability to address this issue largely. Researchers throughout the world are working in this area to develop such a promising tool for utilizing nanotechnology. Various research is in the pipeline, which can provide early diagnosis of tumor cells, type of tumor and exact location in the body (Iqbal et al., 2018). Such diagnosis assists the effective treatment of cancer. Alongside, the targeted nanocarrier system supposedly delivers the chemotherapeutic agents to a particular site of action and thus avoid the damage of healthy cells. Hence, it could be considered as safer therapy than the conventional one which offers patient compliance (Tran et al., 2017). Nanoparticle-based contrast agents are under investigation as a tumor diagnostic agent. Similarly, inorganic nanoparticles, superparamagnetic iron oxide nanoparticles, antibody modified, DNA, RNA, oligonucleotide-modified nanoparticles also found useful in the diagnosis and treatment of cancer are under investigations (Akhter et al., 2013).

IMPACT OF NANOMEDICINE ON PUBLIC HEALTH

Nanomedicine significantly affects various aspects of public health like promotes general health, improves quality of life, increases lifespan, prevents and treats disease conditions and can cure life-threatening disorders. It can also imply for community-based or social health issues including vaccination, infection control, civic sanitization, environmental infection control, early detection and prevention of infectious disease (Oberdorster et al., 2005). The association of school of public health categorized public health into five different core areas including i) epidemiology, ii) biostatistics, iii) health policy management, iv) community and social behavior and lastly v) environmental health science. Epidemiology is concerned with the elements and social distribution of disease while biostatistics deals with the quantitative analysis of factors, frequency, and distribution of disease in society. Subsequently, health policy management prepares guidelines and laws on the basis of community survey to maintain the health of society and improve community health (Oberdorster et al., 2005). Environmental health is based on the effect of the social and physical atmosphere on public health and vice versa. Technological advancements in the medical field always significantly affect public health. Development and implementation of vaccines is the most popular example of advanced medication, which is continuously modified according to the need, and response of the society (Feng et al., 2006; Pradhan et al., 2018). Similarly, now nanomedicines represent an emerging technology, which has the potential to treat untreated chronic disorders like neurodegenerative disorders, cancer, and cardiovascular diseases as well as improve the potency of various drugs. Due to the benefits over conventional therapies such as effective targeting, high performance, prolonged action, and reduced side effects, FDA approved various nanomedicines (Abraxane®, Doxil®, etc.) for the treatment of cancer. Numerous research efforts utilize nanotechnology to improve community health (Pautler and Brenner, 2010).

ETHICAL ISSUES

Concerning about the ethical issues associated with the nanomedicine, one can say that in the present scenario, nanomedicine does not produce any major risk (Resnik and Tinkle, 2007). However, earlier there are some incidences of failure or severe adverse effects were also reported upon human trials. Such contradictions are because the pharmacokinetic response of the human body to a dosage form considerably differs from the animal responses. Thus, it is essential to conduct human clinical trials at the final stage of development before launching the products. In addition, phase IV (postmarketing) trials are recommended by the governing bodies to assure the potency and safety of the nanomedicine. Dose dumping or dose variation is also a major issue with nanoparticles; thus it is essential to monitor the drug dose at initial stages of clinical trials. Moreover, the volunteers of a clinical trial should be previously informed about the safety and risk factors of nanomedicines and a proper consent specifying all the critical terms must be signed by the participant and the company. At the same time, the final cost of nanomedicine is high due to expensive research and development process and application of advanced technologies. This limits the availability of nanomedicines only to the financially stable group of society while unaffordable for the poor population. To resolve this ethical issue, a proper system is needed to relieve the complete industrial control over marketing, fair trade agreement, development of financial support system, an international collaboration to help the needy people and promotional research to develop affordable nanomedicines to reduce the final price (Saraf et al., 2015).

CHALLENGES AHEAD

The synthesized nanoparticles are challenging to get entirely characterized by their safety and toxicity (Wei et al., 2012; Kaur et al., 2014; Khorasani et al., 2014). The relationship between the structure and functions of these Nanoparticles are still to be investigated thoroughly. Many times nanoparticles adsorb the plasma proteins and hence interfere with the body immune system. They may form free radicals, which can also cause genotoxicity.

The cost of the nanomedicines is much higher than the conventional ones because of the use of expensive instruments for its characterization. Moreover, these nanomedicines show an upgraded level of safety as compared to traditional, but health care professionals do not usually recommend upgradation in efficacy level.

Overall, nanomedicines have the fascinating potential to decrease the dose frequency, enhances bioavailability because of its reduced particle size, increased surface area. But, the main concern is about how much that nano-formulation is effective and safe. If any formulation makes pharmacokinetic profile better, but it could not deal with the safety and produces toxicity within the body can be a limitation of nanomedicine.

The production of various nanoformulations such as niosomes, liposomes, and polymeric nanoparticles, require high energy for its processing so that they can overcome stability related challenges such as coalescence and creaming (Maniam et al., 2018). Generally, nanoformulations are produced by either of the two processes that are top to bottom (pulverization, micronization) or bottom to top approach (nucleation). While scaling up the formulation, the major challenge is to control the growth of the particle. This results in batch to batch variation (Mulhopt and Diabate, 2018).

When nanotherapeutic agents like liposomes, nanoparticles are injected within the body, generally produce hypersensitivity reaction triggering the immune-mediated response (51, 52 Walter Brand, 2017). Also, these get accumulated within organs like liver, kidney, and spleen (Fabian et al., 2008; Liu et al., 2009; Park et al., 2014; Zhang et al., 2015).

Liposome tends to hamper the platelets and coagulation factors such as XII and XI resulting in causing thrombocytopenia. Moreover, these react with lipoproteins, extracellular matrix and initiates adhesion and aggregation of platelets (Spagnou et al., 2004; Lv et al., 2006).

FUTURE PERSPECTIVE

Nanomedicines usually play an important role in effective drug delivery. Drug targeting is possible due to these nanomaterials. Both active and passive targeting can be done quickly. In addition, the increased surface characteristics result in efficient drug absorption and hence, can improve bioavailability. However, the two key challenges associated with them is the safety and toxicity profile, which has to be still analyzed critically. The characterization of nanomaterials is another critical challenge where different methods like fluorescence-based assays, cytotoxicity studies are hindered due to the physical and chemical properties of nanomaterials. In the future, it is recommended to focus more on drug loading efficiency as well as minimization of dose dumping. An unexpected immune response is noticed after administering nano formulation, which must be further investigated for its immunotoxicity.

CONCLUSION

Nanomedicines can be considered as a promising way to deliver the drug at the target site. However, the particle size and its distribution should also be kept in mind because these are having the ability to alter the pKa, biodistribution and overall safety of the drug. If the size and size distribution of particles is not within the limit, then the nanoformulations may become antigenic. Moreover, there may be a chance of opsonization of the nanoformulations by plasma proteins that results in phagocytosis, which is ultimately cleared by macrophages. Lastly, these challenges can remain overwhelmed if FDA makes some regulatory guidelines on nanomedicines product development, which should not be similar to the existing product development plans.

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CONFLICT OF INTEREST

The authors have not declared any conflict of interest.

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