Current Challenges and Future Directions in Nanomedicine

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Abstract

Nanomedicine research describes the medical application of nanotechnology and nanoparticle-based drug delivery systems for the treatment of cancer over the past two decades. Nanomedicine is basically a product of a newer scientific technology known as nanotechnology. Nanotechnology is a multidisciplinary scientific field that transforms the pattern of detecting diseases in the human body and also treating the damage. Nanomedicine applies to highly specific medical involvements for the prevention, diagnosis and treatment of various diseases. This developing discipline of nanomedicine brings active pharmaceutical agent and nanotechnology together in order to alter the therapies as well as improve the existing treatment procedures. These nanomedicines are capable of overcoming the biological barriers in the human body to improve the way to deliver the incorporated drug compounds to specific tissues and organs at a predetermined rate. More precisely, nanomedicines have been observed to modify the cellular and tissue uptake of therapeutic compounds and hence improve the biodistribution of compounds to target sites in vivo. In nanomedicine, the active biomolecules and their formulations are manipulated to produce nanostructures of pharmaceuticals of the same size so as to produce predetermined beneficial effect in human beings. These nanomedicines produce an excellent solution for early non-faulty diagnosis of diseases and hence will enhance the treatment of cancer, diabetes, Alzheimer's, Parkinson's and cardiovascular diseases. Nanomedicines have demonstrated several significant therapeutic advantages of biomolecules, however the beneficial clinical translation of these nanotechnology-based biomolecules have not progressed as expected. Hence, in this chapter, current understanding of nanoformulations of bioactives has been exemplified and the challenges are being addressed.

Keywords

Nanomedicine · Nanotechnology · Targeting · Bioactives · Biodistribution · Barriers

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1 Introduction

In recent years, nanotechnology has been increasingly applied to the area of medicine, which is defined as nanomedicine, as a new independent field of life sciences. Nanomedicines for their application in medical field mainly range from the utilization of the nanomaterials for development of nano-systems and biological devices to nano-electronic biosensors and other biological machines. Nanotechnology through nanoparticle-based drug delivery systems basically is emerged as very promising means of treating cancer (Ross et al. 2004). Furthermore, in the last few years, this nanotechnology is getting a great deal of attention due to its tremendous potential in disease diagnostics, monitoring and the treatment. Scientists around the globe from academics and companies are increasing their focus in this globally accepted area.

Nanomedicine is moving in many new directions. Firstly, in tissue engineering, it has been revealed that nanostructure in advanced biomaterials is highly important for how materials interact with the biological interface (Anwarul et al. 2018). Another example includes micro- and nanostructured chip systems for highly sensitive diagnostics, e.g. for detection of disease markers in blood (Shi et al. 2010). The field is progressing at an unbelievable speed, and there is no doubt that many new technologies will be introduced that provide better disease diagnostics and treatments for the benefit of the patients and society in the years to come. Even so, there are also certain challenges that the field faces at a fundamental level. Common to perhaps all technology developments within the field is a poor understanding of the complex interaction between the artificial materials we are developing and the biological environment they are placed in. This lack of understanding is at protein, cellular and whole organism level (Ross et al. 2004; Anwarul et al. 2018). It is clear that surface chemistry, nanoscale to macroscale morphology and material softness are parameters that all affect the biological behaviour of the technologies we are trying to develop, but our ability to understand and map these effects needs to be improved further over the next decades. This point is exemplified by discussing the current understanding of nanoparticle-based drug delivery systems for intravenous administration and their medical application. However, several debates, controversies as well as brainstorming sessions exist among academicians, medicine practitioners and industrial scientists in defining nanomedicines. Several regulatory agencies across the globe have put their views and defined nanotechnology and nanomedicines in various ways. As per the US Food and Drug Administration (USFDA), nanotechnology is the technology which allows scientists to create, explore and manipulate materials measured in nanometres (billionths of a metre) and those materials may differ in terms of their physical, chemical and biological inherent properties. The National Institutes of Health (NIH) in its 'National Institutes of Health Roadmap for Medical Research in Nanomedicine programme' defined nanomedicines as highly specific medical intercessions at the molecular level for curing disease or repairing damaged tissues, such as bone, muscle, other tissues or nerve. Further, Forward Look Nanomedicine programme of the European Science Foundation has comprehensively defined nanomedicine as a medicine which utilises the nano-sized tools, generally under the size of 1000 nm, for understanding the complexity of involved pathophysiology of disease followed by its diagnosis, prevention as well as treatment. The vital objective of nanotechnology and nanomedicines is to improve the quality of living life. Since the last few decades, nanomedicines have come out as the most interesting but promising and much investigated technique in the area of novel drug delivery and diagnostics. This is clear from the fact that a number of promising nanomedicine candidates are approved by different regulatory authorities across the globe like advanced drug delivery, imaging and diagnosis and/or regenerative medicines.

2 Current Challenges

Nanomedicine is expected to provide new breakthroughs to fight several incurable diseases, but for this, a genuine global effort is required to convert the laboratory innovation effectively to their clinical counterparts for the betterment of the human beings. Nanomedicines like nanotherapeutics and nanopharmaceuticals could achieve these important aspects of therapy like diagnosis, improve targeted therapies, reduce side effects and enhance therapeutic monitoring. These advantages will definitely improve the quality of life and be helpful in maximizing the cost-effectiveness of health care. Although nanomedicine has the potential advantages to overcome biological barriers, effectively deliver hydrophobic active entities and preferentially target the sites of infection, the field of nanomedicine is still at its early stage. Most of the nanomedicine research or inventions are still limited to the laboratory phase, and only a relatively small number of nanoparticle-based medicines have been approved for clinical use because of numerous challenges and hurdles at different stages of development (Shi et al. 2010). The first FDA-approved nano-drug formulation is Doxil® in 1995, which can prolong drug circulation time and avoid the RES due to involvement of PEGylation technique. The key feature of this nano-formulation is its stability followed by its ability to release accurate amount of the drug, i.e. doxorubicin at the tumour site (Anwarul et al. 2018; Shi et al. 2010). From 1995 to 2017, more than 50 nanopharmaceuticals have received FDA approval and are currently available for clinical use. The attractiveness of nanomedicine lies in their unique characteristics of three-dimensional assemblance with multiple nanoscale components. At the same time, due to its several complexities, nanomedicine product requires a careful design and engineering, strict characterization of physicochemical properties and validated manufacturing process for reproducible scale-up in order to achieve a consistent product with relatively stable physicochemical characteristics and pharmacological profiles. The safety and regulatory issues of nanomedicine need additional considerations compared with conventional medicines. So, it becomes an important aspect to review and summarise the challenges and limitations during the development followed by commercialization of nanomedicine products as well as to discuss the potential solutions to accelerate the growth of this important field.

Successfully translating nanomedicine from pre-clinical proof of concept to demonstration of therapeutic value in the clinic is still challenging; several obstacles have been identified as top scientific hurdles in bringing nano-engineered products to patients.

2.1 Biological Barriers and Drug Targeting

In order for the drugs to successfully reach the microenvironment of disease sites, nano-based formulation helps them to cross multiple biological barriers (Fig. 27.1).

For example, nanoparticles for oral delivery need to have high stability in the gastrointestinal tract, the ability to penetrate intestinal epithelium and the ability to keep the high systemic bioavailability of drugs after crossing several barriers. Compared with most of the small molecules delivered orally, intravenous administration (IV) is adopted as the only efficient route for delivering of large drug molecule proteins, peptides and polynucleotides. After systemic injection, drugs in circulation still have to overcome various biological barriers to reach their microtargets. The blood-brain barrier (BBB) plays major obstacle for treating the central nervous system diseases, i.e., it forbids almost 99% large and hydrophilic moieties to enter the brain and cerebrospinal fluid and hence brain targeting delivery suffers. There are various possible pathways by which drug-loaded nanoparticles or solute molecules move across the BBB, as shown in Fig. 27.2.

Another most important challenge the formulators encounter is to deliver nanomedicine containing therapeutic agents into solid tumours. Although tumour vasculature is highly heterogeneous in distribution and more permeable in some places, large areas of tumours with high

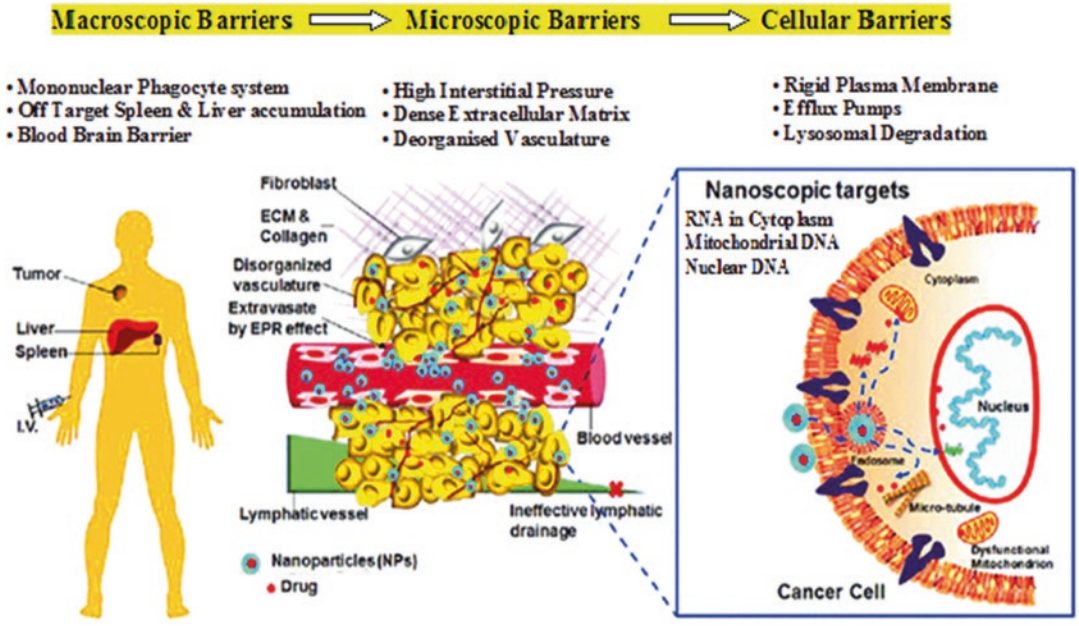

Fig. 27.1 Multiple barriers for nano-formulation

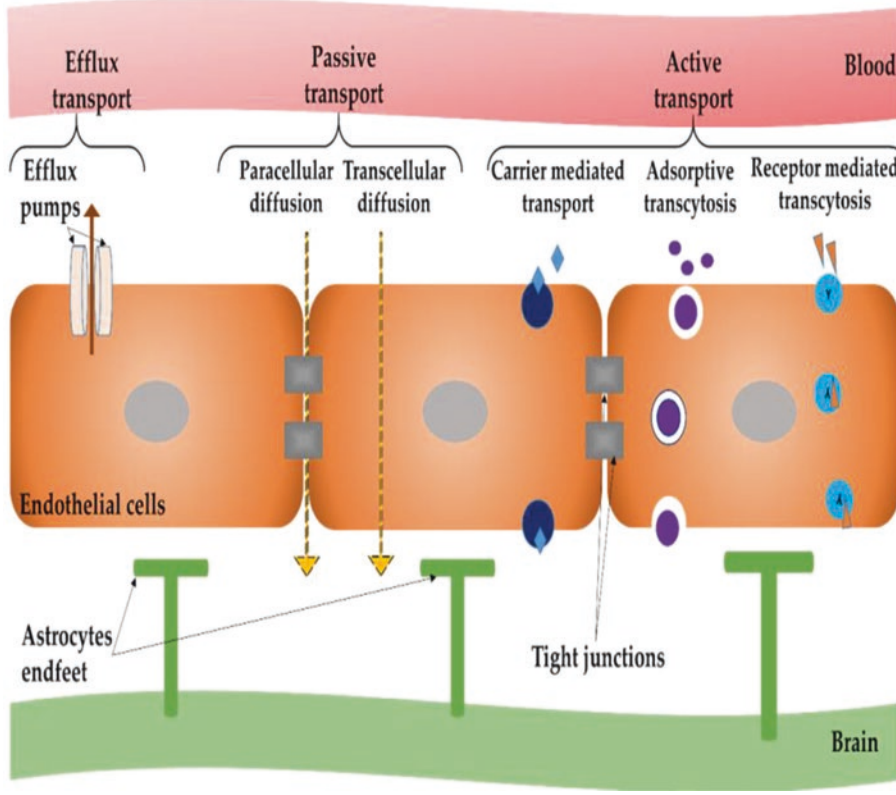

Fig. 27.2 Various pathways through which drug-loaded nanoparticles cross the BBB

cancer cell density and dense tumour stroma are still poorly perfused which further hinder the drug distribution in tumours. In tumour, impaired lymphatic drainage further increases the interstitial fluid pressure (IFP) which further adds another significant barrier to drug delivery and is considered as one of the main factors responsible for reduction in extravasation and transvascular transport of drugs despite the leaky tumour microvasculature and thus restrain the transport of molecules into interstitial space of tumour. Several nanoparticle-based delivery strategies like liposome, polymer micelle and peptide or protein nanoparticles are investigated thoroughly for their capability to deliver drugs.

Tumour vasculature is very leaky and highly permeable, and due to lack of proper lymphatic drainage, the enhanced permeability and retention (EPR) effect develops the accumulation of nanoparticles passively. The macromolecules further accumulated in the tumour microenvironment, and hence tumour drug delivery through EPR noticeably improved. The first marketed nanomedicines were pegylated liposomal formulation containing doxorubicin (Doxil®/Caelyx®) and paclitaxel (Abraxane®). The key issue of this passively targeted nanomedicine is controlling of the pharmacokinetics and biodistribution of nanoparticles by modulating its physicochemical properties. Although passive absorption process has some advantages, but active transport process can reduce the systemic drug exposure by utilizing the active biological transporters. The drugs are effectively targeted to the site of action and hence increases efficacy of the drug.

The active targeting nanoparticles have organized structures that facilitate the incorporation of various targeting active moieties like small molecular ligands for receptors, peptides, proteins, antibodies and oligonucleotides. It can reduce off-target organ toxicities by effectively delivering drugs to the target sites and hence facilitating cellular uptake of encapsulated therapeutic agents (Maeda 2001). Usually the ligands or monoclonal antibodies targeting to the surface receptors overexpressed by cancer cells, such as transferrin receptor (TfR), folate receptor (FR) and epidermal growth factor receptor (EGFR), decorate the surface of nanoparticles to increase cellular internalization of the reagents through endocytosis and improve the efficacy of systemic anticancer therapy (Allen 2002). Additionally, nanoparticles enable the uniform transport of large, biologically active molecules incorporating with protein transduction domain (PTD) and cell penetrating peptides (CPPs); otherwise they cannot effectively enter cancer cells (Maeda 2001; Allen 2002). Moreover, another possible target of nanomedicine is tumour endothelial cells. The cyclic as well as linear derivatives of oligopeptides RGD (Arg-Gly-Asp) bind to the integrins α2β3, αvb3 and α5β1, which provide a tumour penetrating function to the nano-formulations like liposomes and other nanoparticles. With RGD modification, nanoparticles deliver cytotoxic reagents to tumour tissue and achieve significant antitumour effects. The active targeting depends on the affinity and efficacy of a target and its specific ligand. Besides, it is very important to optimize the density of targeting ligands per nanocarrier to achieve not only high targeting efficiency but also to ensure an optimal internalization.

2.2 Analysis and Characterization of Nano-formulations

In comparison with the conventional pharmaceutical formulations, nanomedicine is a complex alternative consisting of other different components which rather serve to a specific function. So, identifying and characterizing those excipients along with active ingredient is very much essential and for this purpose more sophisticated, and appropriate analytical testing methods are required to characterize as well as quantify each formulation component. Furthermore, the interactions between these components and with the active ingredient/s including both physicochemical properties and biological behaviours are also to be investigated. So, it now becomes a challenge for the formulators to develop nanomedicine not only for its technical aspect but also the regulatory perspective. In general, the most important physicochemical features of nanomed-

icine are structure, particle size, size distribution, surface properties, surface charge, porosity and overall stability which are rather difficult to characterize in the developed nanomedicine products because of their changeable properties. Taking polydispersity (PD) as an example, it is an important parameter relating to the heterogeneity in terms of size, shape or mass of particles. So, if the developed nanomedicine formulations have the same average size but with different PD, it may lead to noticeable changes in the fate of the formulations like drug release rate, biocompatibility, stability and in vivo behaviours including their targeting properties and toxicity. Another problem the formulator usually encounters is stability characterization of nanomedicine. Biodegradable and biocompatible lipids and polymers have been widely used for the development of nanomedicine products due to their excellent physicochemical features. But this biodegradable property of these materials will also change due to the involvement of processing parameters like temperature, pH, etc. which in turn alter the properties of nanomedicine products during the storage either in the solutions or even in a lyophilized powder form. So, it is important to improve quality assessment of those biodegradable materials through validated and reproducible standards. In vivo biodistribution is another frequent issue of the nanocarriers over time. After administration in vivo, nanomedicines would reach biological fluids and may interact with biomolecules (e.g. proteins) or biological fluids (e.g. blood serum), which could significantly alter their physicochemical properties such as size, aggregation or agglomeration, and release profile and alter the function of nanomedicine in biological systems. It is indispensable to characterize completely the nanomedicine products under clinically relevant environments using in vitro and in vivo models in order to establish in vivo-in vitro correlation.

Nowadays although pictorial biodistribution of nanoparticle as well as their accumulation in bio-models can be obtained by using fluorescence or radiolabelling method, still it is very hard to assess the mass-balance information which is important in order to account the full administered dose and also to ensure safety and hence toxicity. Furthermore, the radiolabelling and fluorescence emitters are conjugated chemically to one of the formulation compositions of nanoparticles, which is not always stable in the internal environment and easily degraded. Therefore, it may lead to unreliable as well as variable results by tracing the degraded fluorescence or radiolabelling moiety instead of the drug or the nanoparticle as a whole. Additionally, it may be predicted that the distribution pattern of this chemically modified nanoparticles may be different in comparison with the same nanoparticles without radiolabelled or fluorescence modification. Last but not least, nanomedicine with more than one composition and the ability to carry and deliver multiple therapeutic and imaging agents may require individual tracking.

Thus, various characterization methods including the quantification of active and inactive ingredients along with the impurities, measurement of particle size and size distribution with light scattering, surface charge determination, imaging of nanoparticles by microscopy and new advanced techniques specifically to characterize the in vivo behaviours of nanoparticle are very much essential to ensure and establish that the developed nanomedicine formulations have all the desired properties for the intended therapeutic effect and reproducible efficacy with minimum side effects.

2.3 Scale-Up and Manufacturing

The most challenging problem in the development of pharmaceuticals is controlling key parameters along with the stability on a batch-to-batch basis and its applicability. Small-scale processes of nanomedicines may achieve reproducibility with well-characterized nanoparticles and their preclinical as well as clinical study results may be up to acceptable level. But in large-scale production, the physicochemical processes of the nanomaterial are found difficult to control, which in turn lead to batch-to-batch variations and failure in preclinical and early clinical studies. Most of the nano-formulations

including nanoparticles are three-dimensional complex products with specific components. Due to these multicomponent systems along with their special arrangement, the control over manufacturing process is very challenging. All of these factors make the manufacturing and scale-up of nanomedicine difficult. The first FDA-approved nanomedical therapeutics Doxil® also suffered the same issue which subsequently had to be suspended in November 2011 because of its manufacturing and sterility issues. The shortages of Doxil® were until 2014, and a different manufacturing method for Doxil® was adopted which subsequently increased the cost of medication. Properly identifying the components and understanding their interactions in the early development are required to ensure reproducibility of the product during the larger-scale 'manufacturing. In general, there are two preparation methods for nanoparticles like 'top-down' and 'bottom-up' approaches. Top-down methods manufacture nano-entities by grinding the larger particles using the milling technique, while bottom-up methods arrange and rearrange the smaller components into functional assemblies like monomer polymerization, etc. (Ferrari 2005). Several techniques like high-speed or high-pressure homogenization, sonication, milling, cross-linking, emulsification, organic solvent evaporation, centrifugation, filtration and lyophilization are always employed for manufacturing of nanomedical formulation. It becomes an important factor to select the suitable approaches and processing parameters in order to scale up the nanomedicines. These parameters may involve the molar ratio of nanomaterials, active ingredients, the excipients and the targeting moieties, the type of organic solvent and emulsifier/cross-linker/stabilizer, pressure, operating temperature and pH (Ferrari 2005). Choosing and considering the incorrect conditions could lead to altering the chemical structure of the therapeutic reagents and unpredictable impurities. Particularly, it is quite feasible enough to change chemical structure and its conformation of macromolecules like peptide and protein, by cross-linking, degradation, denaturation and coagulation. Hence the manufacturing of nanomedicine is not that simple, rather a well-defined, precise, validated production steps with strict control of quality imparting parameters are required. The relatively high raw material cost along with the need for sophisticated equipments and multistep production process also become hurdles for the manufacturing and scale-up of nanomedicine, which makes the production of nanotherapeutics very expensive. Therefore, in order to compensate the high developmental and manufacturing costs on nanomedicine products, the clinical effectiveness of nanomedicine drugs is more demanded than conventional available therapeutics. These factors may deter pharmaceutical companies from carrying out the large-scale production of nano-formulations.

2.4 Pharmacology and Safety Challenges

Physical as well as chemical characteristics of nanomedicine remarkably influence the pharmacological benefits as well as the safety profiles. Even in small changes composition and subtle alteration in the final manufactured products could result in significant changes in pharmacology and toxicity of nanomedicine (Couvreur and Vauthier 2006). The basic requirement to achieve the desired pharmacological profile of a successful pharmaceutical including nanomedicine is to design pharmacokinetic parameter of the formulation. Moreover, most of the researcher and pharmaceutical companies use the standard criteria of drug molecule to the assessment of nanomedicine. This is because active entities of small molecular size normally diffuse through biological barriers more readily, and hence at equilibrium the drug concentration in the blood is maintained to achieve the target tissue levels. Furthermore, the measurement of drug concentration in the plasma becomes an important criterion to determine PK and hence the fate of any pharmaceutical formulation. However, if this methodology is applied to nanomedicine, it cannot be presumed to be accurate and could be intrinsically flawed. Accordingly, different PK approaches with different indications are required

for different nanomedicines. For example, instead of the standard method to quantify the drug behaviour in plasma, the pharmacological parameters at the specific target site could be more relevant to evaluate and accesses the therapeutic action of nanomedicine products and the reproducibility as well. Furthermore, the bioequivalence of nanotechnology-based pharmaceutical products could be used to evaluate their effectiveness as well as to address toxicity issues for human health. The nanoscale size of nanomedicine products can simulate the intracellular biomolecules like polysaccharide, protein and enzyme involved in cell signalling, which may lead to unfavourable biological interactions. The nanotoxicology is an independent field of research now, and numerous data relating to the toxicity of different nanoparticles are available. On the other hand, the toxicity of nanomaterials remains difficult to evaluate, especially its long-term toxicity as because the classical drug toxicity assay determination for these nanomedicines may be inadequate. And there is no standard list of required tests. Thus, the search for advanced complementary assays along with the standard criterion for toxicity evaluation of products of nanomedicine becomes emergent. There are multiple properties, such as size, shape, surface charge, surface area, porosity or hydrophobicity, which affect the performance of nanomedicine drug and nanoproducts at the nano-bio interface. Thus, every nanomedicine product may have their own different issues and, hence, require particular and different evaluations. The term toxicity in pharmaceutical industry usually refers to chronic toxicity and acute toxicity. Chronic toxicity is a time-consuming study, and analyzing these chronic toxicity data is more demanding. Due to the unavailability of suitable animal model, immunotoxicity sometimes cannot readily carry over from in vitro testing to humans. On the other hand, acute toxicity generally includes haemolysis, oxidative stress, inflammation, impaired mitochondrial function or complement activation. Nanoparticles themselves and the biologics such as proteins, peptides, antibody fragments and nucleic acids in nanoparticles can serve as antigen sources that can provoke the immune response. The immunogenicity of nanoparticles can also be affected by their physicochemical properties, such as size, charge, solubility, surface characteristics and hydrophobicity.

2.5 Regulatory Challenges

Although the USFDA and European Medicines Agency (EMA) approved a number of nanomedicinal products for cancer therapy, there are not specifically implemented guidelines for drug products containing these kinds of materials by the FDA, EMA and by other regulatory bodies yet. The lack of information in the examination of nanomedicine products or nanomedicine therapeutics can only make regulatory decisions based on individual benefit and risk assessment (Jain 1994). As such the regulatory process is time-consuming and requires a high-level expert in innovative technologies, which may result in regulatory delays. Furthermore, regulatory issues are vital for the development of cutting-edge technologies to quantify or characterize and also to monitor the quality of nanomedicine products besides clinical trials and the approval process. Hence, there is an urgent requirement for elaborated regulatory guidelines for characterization and quality control as well as accessing the safety issue of nanomedicine products (Jain 1994). However, the definitions, guidelines and cooperation in this area are gradually established and improved. FDA has released the guidance for industry for nano-formulations, FDA-Regulated Product, in June 2014, in which nanomaterials are defined as engineered materials with dimension between 1 nm and 100 nm. The FDA and European Technology Platform on Nanomedicine (ETPN) further intend to work together with the Nanotechnology Characterization Laboratory (NCL) and European Nano-Characterization Laboratory (EUNCL), respectively, to promote the regulatory pints for characterizing nanomedicine products. The vital demand for regulatory agencies in nanomedicine therapeutics is to refine and standardize requirements for the approval of safe nanomedicine products. Along with the above controls and reviews, more advanced and multifunctional tools need to be developed to

characterize the complexity so that the approval process of nanomedicines could be improved.

3 Future Direction of Nanomedicines

Recently, the research on the application of nanomedicine is much more overvalued with huge number of patents and published research articles. However, the factual potential of this novel technology could only be measured by the approval of regulatory authorities followed by the genuine acceptance of the public around the globe. Both these factors, i.e. regulatory approval and public acceptance, play very significant role for the commercial success of nanomedicines. According to a recent research, the nanomedicine industry is treasured worth more than $150 billion worldwide. Further, it was speculated that the nanomedicine market especially related to anticancer products would grow more than 15% over a couple of years; it was further estimated that in the time to come, nanomedicine specially central nervous system products as well as anticancer products will dominate the market by contributing almost 40% revenue.

Nanotechnology is now in the floor to change the scale and methods of vascular imaging and drug delivery inside the biological system. The NIH (National Institutes of Health) Roadmap's 'Nanomedicine Initiatives' predicts that nanotechnologies will provide more medical benefits within the next 10 years. This includes the advancement of laboratory-based nanoscale diagnostic and drug discovery devices such as microchip devices, nanopore sequencing, etc. The National Cancer Institute has also similar programmes, i.e. production of nano-based multifunctional entities which can not only diagnose and deliver therapeutic agents but also monitor the progress of cancer treatment. These include engineering and designing of targeted contrast agents that improve the resolution of cancer cells to the single cell level along with the nanodevices capable of detailing the biological and evolutionary range of the multiple cancer cells which make up a tumour within an individual. Thus, nanocarriers may furnish the complete potential of nanotechnology in targeted imaging and drug delivery in vivo condition by correlating the physicochemical and physiological processes. So, a complex interaction begins for a nanovehicle and its microenvironment, for example, carrier stability; intra- and extracellular drug release rates in different pathological conditions; interaction with biological environment, such as opsonization; and other huddles like anatomical, physiological, immunological or biochemical en route to the desired target site and tissue-specific receptor expression and escape routes from the vasculature. Characteristically, the carrier design and their targeting strategies may vary in relation to the type, developmental stage and location of the disease. Further, the toxicity issues are very well-known concern, but are generally ignored. Therefore, it is very much essential that fundamental research shall be carried out to address these issues if application of these nanotechnologies is to be achieved. The future of nanomedicine will depend on the rational of development of several materials for designing the nanotechnology and sophisticated tools based around an efficient and thorough understanding of biological processes rather than forcing applications for some materials currently in vogue.

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