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Review

Recent trends of nanomedicinal approaches in clinics

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ABSTRACT

Nanotechnology has become the indispensable cutting edge science providing solutions to many problems associated with human being. The application of nanotechnology associated to human health "nanomedicine" has revolutionized the drug delivery system by providing improved pharmacological and therapeutic properties of drugs. These advantageous effects of drug loaded nanocarrier systems are embraced by the pharmaceutical industries for the development of different effective nanocarriers. Currently, several drug loaded nanoformulations are approved by the Food and Drug Administration (FDA), and some of them are undergoing clinical trials for the human use. In this review, we have discussed the progress achieved so far for various drug loaded nanoformulations along with few emerging nanoformulations that are about to enter into clinical trials.

1. Introduction

Nanotechnology is a multidisciplinary field which amalgamates science and engineering for the creation of material or system in the nanometer (nm) scale at the level of atom, molecules, and its macromolecular structure (Sahoo and Labhasetwar, 2003; Whitesides, 2005). The prefix "nano" is derived from the Greek word "dwarf". One nm is equal to one-billionth of a meter, which is also about the width of six carbon atoms or group of ten water molecules. The physics and chemistry of bulk materials behave differently in terms of strength, conductivity and reactivity when they are reduced to nanoscale. The application of nanotechnology has been wide spread and much integrated to human health. Various developed nanomaterials are making their ways into our lives in the pharmaceutical and medical applications. For an instance, currently there is no cure and preventive measures for HIV/AIDS but with the help of advancement of nanotechnology various treatment options are now emerging (Mamo et al., 2010). Similarly, cancer and tuberculosis top the list of dreaded diseases in developing countries and with utilization of nanotechnology based formulations tremendous progress towards therapeutic efficacy against these diseases has been achieved (da Silva et al., 2016; Hare et al., 2017). Nowadays, nanotechnology is extensively used in consumer goods, vehicle manufacturers, cosmetic industry, military products etc. For example, in sunscreen lotion, nanoparticles of titanium dioxide and zinc oxide are used which act as a reflector of the harmful sun rays (Newman et al., 2009). Nanotechnology has also varied application in the food industry where various polymers are actively used for the improved food packaging. Recently, polymer nanocomposites (like silica nanoparticles, silicate nanoplatelets, carbon nanotubes, graphenes, starch nanocrystals, chitosan nanoparticles etc.) are the latest materials created which provides flame resistance, better thermal property for enhancing the shelf-life and durability of the packaged food (Duncan, 2011). Similarly, silver nanoparticles are also used owing to their broad spectrum antimicrobial property in food storage bins for safeguarding against food spoilage due to microbial growth (Rhim and Ng, 2007). In textile industry, clay nanoparticles are incorporated in nylon fabrics for the flame retardant property. The nanosilica along with maleic anhydride acts as catalyst for the improvement of wrinkle resistance of silk (Song et al., 2001). Nanocomposite fibers such as, graphite nanofibers, single-wall and multi-wall carbon nanotubes (CNTs), nanosilicates and metal oxide nanoparticles are extensively used in automotive, aerospace and military applications (Schnorr and Swager, 2010). The nanocomposite fibres are evenly distributed in polymer matrix which increases the toughness and makes it abrasion resistant (Sennett and Welsh, 2003). Apart from that, novel CNTs are also developed for multifunctional textiles for providing superior strength, light weight with high electrical conductivity (Schnorr and Swager, 2010). Cerium oxide nanoparticles have been effectively used in advanced technologies as catalytic agent, solid oxide fuel cells, oxygen sensor, high-temperature oxidation protection material and as a component in solar cells (Asati et al., 2009; Martínez-Arias et al., 2005). Besides the commercial application of nanotechnology, this upcoming branch of science has also made its impact in environmental application. The futuristic application of nanotechnology to the environment i.e. "Green Nanotechnology" envisages sustainability to address global issues like energy shortages, scarcity of clean water, and many other

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allied areas (Goel and Bhatnagar, 2014). Green nanotechnology uses the principles of green chemistry, green engineering and industrial ecology to make eco-friendly nanomaterials without toxic ingredients and consumes less energy during the manufacturing process (Goel and Bhatnagar, 2014). Over the years, the promising field of nanotechnology has evolved tremendously exhibiting huge potentialities in diverse areas including human health sector (Sahoo et al., 2007). Nanotechnological application in the field of medical sciences and diagnostics focuses on a major aspect regarding the proper delivery of drugs, diagnostic agents and different therapeutic agents inside the body (Sahoo and Labhasetwar, 2003).

Introduction of nanotechnology has revolutionized the drug delivery aspect towards the therapy and diagnostic under the arena of nanomedicine. The term “nanomedicine” has been coined for the applications of nanotechnology for the treatment, diagnosis and monitoring of disease related to human health (Rizzo et al., 2013). Nanotechnology based approaches provide an opportunity to design novel formulations for the major benefit towards healthcare setting. Nanotechnology scientists are continuously developing pharmaceutical products for different diseases imposing significant impact on current practice of medicine, which in turn enhances patient’s quality of life (Rizzo et al., 2013). Nanotechnological platforms improves drug delivery that are based on several factors of manoeuvring like aqueous solubility, high surface area, control of particle size, biocompatibility, stealth property, target specificity, controlled release etc. (Moghimi et al., 2005; Sahoo and Labhasetwar, 2003). These unique characteristic features of the nanocarriers provide higher therapeutic efficacy, extended plasma half life that lowers the frequency of administration and creates an opportunity to deliver two or more drugs simultaneously as a combination therapy inducing the synergetic effect. Such modality can overcome the shortcomings of the monotherapy by acting upon diverse signaling pathways as well as suppressing multi-drug resistance for an effective therapy (Parhi et al., 2012). According to the market research report of business communication company (BCC) the estimated global nanomedicine market has reached $63.8 billion in 2010 and $72.8 billion in 2011 (Fontaine et al., 2012). With passage of time, several discoveries are continuing in the areas of nanomedicine. Various pharmaceutical companies and academic researchers across the world are exploring this new strategies as an advantageous step for the drug delivery systems (DDS) (Hafner et al., 2014) .If this trend continues then the global nanomedicine market will exhibit a compound annual growth rate (CAGR) of 12.5% between 2015 and 2023 according to the transparency market research .

Over the last two decades, large number of nanomedicines have received regulatory approval as therapeutic and diagnostic agents for the treatment of different cancers (solid tumors and haematological malignancies) and other diseases like; asthma, pain, allergy, infection, high cholesterol, autoimmune disease, fungal infections, macular degeneration, hepatitis etc. (Brannon-Peppas and Blanchette, 2004; Kawasaki and Player, 2005). The approved nanotherapeutics products enlisted in Food and Drug Administration (FDA) agency of United States of America or other related foreign agencies, provide tremendous hope for betterment of human health care. Further ongoing developed nanotechnological products, which are under preclinical and clinical trials are entering the pipeline for venturing into the pharmaceutical market. Looking at the enormous scope of nanomedicine, this review mainly focuses on the developed nanocarriers for drug delivery, gene delivery and diagnostic applications of human health.

2. Role of nanotechnology in clinical application

Drug delivery phenomenon is a challenging aspect of pharmaceutical sciences, where the pharmaceutical drug molecules face numerous challenges after being delivered either parenteral or through an oral route of administration. Post administrations in body, native drugs are subjugated to wide spectrum of internal harsh conditions. Further, presence of different physiological/biological barriers results in suboptimal concentration of the administered drug at the disease site contributing its low efficacy (De Jong and Borm, 2008). The internal physiological condition such as pH, enzymes and intestinal epithelial barriers mostly regulates the intrinsic concentration of the native drug (Parveen and Sahoo, 2008). In this context it has become crucial to devise strategies for the optimal actions of the therapeutics leading to their clinical effectiveness. Drug delivery and related pharmaceutical progress in the milieu of nanomedicine have emerged as the front runners in providing a safe and effective delivery system (Moghimi et al., 2005; Parveen et al., 2012). Basically, the primary objectives of nanoformulations in drug delivery include: (1) precision in targeting and delivering the drug at desired site (2) biocompatibility (3) diminution in toxicity to the normal cells at the same time maintaining therapeutic effectiveness at the desired site (De Jong and Borm, 2008). The engineered nanoformulations increase the aqueous solubility and shield the encapsulated drug thereby preventing its untimely degradation owing to harsh physiological conditions, this elevates the plasma half life of the drug and that in turn regulates their activity. Moreover, the ability of these drug carriers to demonstrate a sustain release phenomena contributes in providing an optimal concentration of drug at disease site in a sustained release manner which prevents the administration of elevated dosages of drug that in turn regulates high toxicity. Additionally, the prospect of site specific release by nanocarriers prevents nonspecific delivery at healthy sites that contributes in regulating toxicity (Fig. 1).

Currently, with the emergence of nanotechnology, different novel drug delivery carriers were developed with the help of biocompatible and biodegradable materials that can significantly be supportive in clinical application (Kayser et al., 2005; Parveen and Sahoo, 2006). In the domain of drug delivery, two different ways (i.e. passive targeting and active targeting) are explored by which the formulated nanoparticles reach the diseases’ sites (Fig. 2). Passive targeting takes the advantage of the inherent size of the nanoparticles and exploits the unique anatomical and pathophysiological abnormalities of tumor vasculature for delivery of payload at requisite site. The nanoparticulate carriers are endocytosed and retained in the tumor tissues by exploiting the hyperpermeable tumor vasculature and impaired lymphatic drainage system resulting in “enhanced permeation and retention (EPR) effect (Acharya and Sahoo, 2011). However, in order to utilize the physio-pathological and anatomical peculiarities of the tumor tissues, the nanocarriers necessitate prolonged circulation in the blood stream. The durability in the bloodstream of nanocarriers is affected by interactions with specific blood circulating components identified as opsonins that results in a conformational rearrangements that induced detection by mononuclear phagocytic system (MPS), through specific membrane receptors (Salmaso and Caliceti, 2013). Thus, surface opsonisation promotes removal of particles from the circulation which may reduce the availability of the drug at the desired site. To bypass the MPS, most passive targeting nanocarriers are surface coated with polyethylene glycol (PEG) a process called PEGylation, for providing “stealth” property (Davis, 2002). Coating of PEG onto nanocarriers reduces the adhesion of opsonins on the nanoparticles making them invisible to phagocytic cells and hence their clearance from blood circulation is evaded (Salmaso and Caliceti, 2013). At present although most clinical trials for anticancer therapy rely on passive targeting, due to its limitation another strategy is being developed to maximize the accumulation of nanoparticles at the preferred site of interest. In order to exploit the increased accumulation of nanoparticles at the diseased site, “active targeting” is adapted that is based on specific ligand-receptor recognition type of delivery (Figure-2). Receptors utilized in this modality are particularly over-expressed in the tumors or diseased tissues while the ligands for specific receptors are conjugated onto the nanoparticulate formulations. Following recognition by receptors on specific cells, these ligand conjugated nanocarrires are endocytosed by receptor mediated endocytosis (Das et al., 2009; Torchilin, 2007), that