Review:

Chitosan Nanoparticles for Effective and Safe Drug Delivery: Potential Big Deal in Intellectual Property Business

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Abstract: According to the world drug report 2016 of United Nations Office on Drug and Crime, over 29 million people who use drugs are estimated to suffer from drug use disorders. It is estimated that 1 in 20 adults, or a quarter of a billion people between the ages of 15 and 64 years, used at least one drug in 2014. The estimated 207,400 drug-related deaths in 2014 is corresponding to 43.5 deaths per million people aged 15-64. The number of drug-related deaths worldwide has also remained stable, although unacceptable and preventable.

The use of conventional antimicrobial agents against infections is always associated with problems such as the development of multiple drug resistance and adverse side effects. In addition, the inefficient traditional drug delivery system results in inadequate therapeutic index, low bioavailability of drugs, inefficient delivery of the drugs, causing systemic side effects, problems of poor uptake and destruction of drugs (when orally administered).

One of the most dynamic research areas in the field of nanotechnology is nanomedicine and target drug delivery is one of the highly specific medical interventions for prevention, diagnosis and treatment of diseases. Problems associated with conventional drug administration methods may potentially be overcome by these novel drug delivery methods. Researchers have been able to develop targeted and sustained drug delivery platforms harnessing unique physicochemical properties of nanoparticles. Advances in research on biocompatible polymeric nanoparticles have enabled more efficient and safer delivery of drugs with improved pharmacokinetics and pharmacodynamics with reduced side effects. Total market size of nanotechnology in drug delivery in 2021 is forecasted to be US$136 billion. Trends also suggest that the number of nanotechnology products and workers worldwide will double every 3 years, achieving a US$3 trillion market with six million workers by 2020. Chitosan nanoparticles seem to be the most promising nanoparticle that can be used for developing multipurpose drug carrier platforms due to its biocompatibility, mucoadhesivity, non-toxicity and biodegradability.

Despite of potential benefits of nanoparticles in target drug delivery, there are certain engineered nanomaterials which can lead to unforeseen environmental, health and safety risks. Therefore, adequate attention is needed from the beginning in order to ensure sustainable nanotechnology. This review article is focused on frontier research, toxicity evidence and patent filing trends in applications of chitosan nanoparticles with an emphasis on target drug delivery.

Keywords: Biocompatible, Chitosan nanoparticles, Hazards and risks, Nanomedicine, Nanotechnology, Patents, Pharmacodynamics, Pharmacokinetics, Targeted drug delivery.

I. Introduction

A. Background

In contrast to the very smaller size of the nanoparticles, the scale of their applications is tremendous. Nanotechnology is a platform of technology encompassing and influencing a wider spectrum of other technologies including materials, engineering, healthcare, pharmaceuticals, agriculture, energy, environment, electronics and information and communication technologies. Even though different applications of engineered nanoparticles have potential to yield socio-economic benefits, there are concerns on potential hazards and risks of same in terms of environment, health and safety. Researchers and scientists in leading research organizations and universities around the world have been exploring potential applications of engineered nanoparticles especially in the field of medicine. Chitosan nanoparticles, being a biocompatible, biodegradable and non-toxic polymer will play a significant role in bringing

economically sound socially and environmentally responsible innovations in the field of nanomedicine in future.

B. Objectives

The objectives of this article are to:

- Explore current status of research towards application of nanoparticles in nanomedicine and potential hazards and risks of engineered nanoparticles.
- Analyze patent information and trends pertaining to application of chitosan nanoparticles in target drug delivery.
- Identify knowledge gaps and provide recommendations on;
  - Future research in the field of nanoparticle mediated target drug delivery.
  - How to deal with related Intellectual Property.

C. Methodology

This article is based on an extensive review of literature published in the period from 2003-2016. The selected literature comprised mainly of scientific publications, conference proceedings and patent data were also used.

D. Frontier R&D towards Application of Nanoparticles in Medicine

a) Nanoparticles for Early Detection and Effective Treatment of Cancers

According to the World Health Organization (WHO), there will be 15 million new cases of cancer worldwide in 2020. More than 90 % of cancer-related deaths occur by the spread of malignant cells to vital organs, a process called metastasis. Use of targeted delivery of specific nanoparticles into the tumor can trigger cancer biomarker production to a detectable level and thereby to detect tumors as early as possible to treat same effectively.

Nanoparticles can be transported into the tumor and then activated to produce heat and destroy only cancer cells without harming healthy living cells. The existing chemotherapy drugs can be encapsulated in nanoparticles which allow much more localized delivery reducing significantly side effects on healthy cells and tissues**.** Vijayakumar and Paulsi (30) observed utilizing gold nanoparticles for early detection and therapeutic activity of cancer. The efficacy of cancer drugs is often limited because only a small fraction of the administered dose accumulates in tumors. Xu *et al.* (33) found an injectable nanoparticle generator (iNPG) that overcomes multiple biological barriers to cancer drug delivery. In most cancer cases, the immune system ignores cancer cells as it cannot tell the difference between these and healthy cells. This makes it vital to give the immune system the ability to recognize and target cancer cells. Kranz *et al.* (9) developed a vaccine using different types of RNA-containing nanoparticles disguised in fatty acid coatings that worked best to reach the relevant parts of the immune system. Yang *et al.* (34) investigated polymer-lipid hybrid nanoparticles for targeted drug delivery to human breast cancer cells.

b) Nanotechnology to Fight against Infectious Diseases

Application of nanotechnology in pharmaceuticals and microbiology facilitates new strategies to prevent infectious diseases effectively by coatings and filtration. Nanoparticles mediated delivery of existing antibiotics enhances their bioavailability and increase target specificity. By combining nanoparticles and antibiotics makes them more lethal for microorganisms.

c) Nanoparticles to Fight against Diabetes

The lifelong injection of insulin in late type 2 diabetes mellitus affects patients' quality of life as it is invasive, painful and hence particularly difficult for small children. It does not allow complete control over the glucose level. In worst case scenario, it leads to neurologic or vascular disorders. Sharma *et al.* (25) observed nanoparticle based insulin delivery system as the next generation efficient therapy for Type 1 diabetes. Woldu *et al.* (32) identified nanoparticles as new era of diabetes management. Nanoparticles from biodegradable polymers (chitosan, alginate etc.) have been used as a carrier for oral insulin delivery. Nanoporous membrane and biodegradable polymeric nanoparticles are used for parenteral insulin delivery.

Recent research is focused on developing nano-based innovative sensor systems for improved non-invasive or less invasive monitoring of glucose level in the blood. Researchers are also studying on delivery of insulin in the form of nanoparticles into the nose, or into lungs as a spray, or through the gastrointestinal tract as a pill as non-invasive and painless application routes by aid of nanoparticles.

d) Iron Oxide Nanoparticles for Cancer Imaging with Enhanced Accuracy

Magnetic iron oxide nanoparticles engineered with a specific coating can bind to the tumors. Their magnetic properties make them suitable imaging agents for MRI scans with a very high resolution and an accurate mapping of lesions enabling surgeons to select patients and remove the tumors effectively. Peng *et al.* (17) highlights although recent advances have demonstrated the feasibility of using targeted magnetic iron oxide nanoparticles for tumor imaging and therapy, methods and strategies to produce tumor-targeted imaging probes with a high specificity and sensitivity are still greatly needed.

e) Nanofibers for Tissue Engineering

Nanofibres can potentially be used to fabricate scaffolds having resemblance to the architecture of natural tissues. Researchers and engineers have developed chitosan based nanocomposite martial with desired chemical and mechanical properties for tissue engineering. Nevertheless, Gao *et al.* (5) argues that there are lots of room for improvement in mechanical properties

and biocompatibility of chitosan before it becomes an ideal biomaterial for biomedical and tissue engineering applications.

f) Nanoparticles for Ophthalmological Treatment

Superficial barriers for effective eye treatment include the ocular surface epithelium and the tear film, and internal barriers include the blood-aqueous and blood-retina barriers. Innovative formulations of nanoparticles as eye drops can be used for ophthalmological drug delivery. Chitosan nanoparticles and natural lipid nanoparticles will be ideal as these are biocompatible materials. Calonge (2) observed nanocarriers permit the non-steroidal anti-inflammatory drug indomethacin to reach inner eye structures using the transmucosal route.

g) Nanoparticles for Infections from Antimicrobial-Resistant Bacteria

Nanoparticle mediated antimicrobial peptides (AMPs) have potential to be used against infectious diseases as they are less prone to induce resistance. Development of multi-drug-resistant bacteria is one of the greatest challenges for healthcare practitioners and is a significant global threat. Nanomaterials have potential in both the medical and veterinary fields. Several nanostructures comprising metallic particles have been developed to counteract microbial pathogens. Rudramurthy *et al.* (23) observed development of effective nanomaterials requires in-depth knowledge of the physicochemical properties of nanoparticles and the biological aspects of microorganisms.

h) Nanoparticles for Early Detection of Alzheimer Disease

At present, the challenge in treating Alzheimer disease is how to carry out early diagnostics for effective treatments at its initial stages, before irreversible brain damage or mental decline is occurred. Specially engineered nanoparticles are being considered as a useful alternative to diagnose and treat neurodegenerative diseases as nanoparticles can transport across the blood-brain barrier.

i) Nanoparticles for Diagnosis and Therapy of Arthritis

Nanoparticle assisted magnetic resonance imaging (MRI) allows very high resolution, and accurate detection of distinct patterns of inflamed joints enabling effective treatment of Rheumatoid Arthritis and quantification of the effectiveness of the treatment.

II. Why Nanoparticles are Promising in Drug Delivery?

Conventional drugs have low solubility and unstable compared to targeted drug delivery systems. Conventional drugs also have poor absorption, shorter half-life and require large volume of drugs. The third reason constitutes the pharmacodynamic properties of drugs. The conventional drugs have low specificity and low therapeutic index as compared to targeted drug delivery system.

Functionalized nanoparticles (including fluorescent, radioactive, paramagnetic, superparamagnetic and liposomes etc.) can be used as diagnostic and therapeutic moieties for site-specific delivery of drugs. Coating of the particles and functionalization of their surfaces can be done to impart characteristics namely hydrophobic, hydrophilic, lipophilic, mucoadhesive etc. which enables it making biocompatible and ensure a highly selective binding to the desired target. Nanoparticles can be functionalized to mimic the size, shape, and surface of the natural high-density lipoproteins found in the blood for therapeutic purpose.

Nanoparticles show exceptional physicochemical characteristics due to its large surface area to volume ratio and interact with cell membrane receptors, peptides etc. These characteristics can be harnessed to design multipurpose drug delivery platforms to deliver drugs in controllable and sustainable manner. They can be used to target specific cells with high specificity and affinity. Nanoparticles can penetrate endothelium, entered into blood vessels due to its smaller size and deliver drugs to predefined site. There is also a potential for nanoparticles to be used in simultaneous diagnosis and treatment of diseases with significant cost reduction and time saving compared to conventional diagnosis and drug delivery methods.

Biological mechanisms in the human body is in the range of nanometer which allows nanoparticles to penetrate through natural barriers enabling access to new sites of delivery and to interact even with small proteins in blood stream, organelles, cells or tissues.

Nanoparticles could even provide efficient delivery systems for DNA vaccines as long term extension of gene therapy with localized treatment for some genetic diseases. The nanoparticles protect the vaccine, allowing the vaccine time to trigger a stronger immune response. Creation of self-assembling biomolecular nanostructures resemblance to nanoparticles as a cancer vaccine might be possible.

Nanoparticle mediated drug delivery offers many advantages over the conventional delivery system as follows:

- Controlled and sustained release of the drug at the site of infection, thus increasing the therapeutic efficiency of the drug, minimizing the systemic side effect and lowering the frequency of administration.
- Specific functionalization enables controls of bio distribution.
- Pharmacokinetics of a drug can be modulated to desired level.
- Drug can be incorporated into the system without any chemical reaction, thus preserving the drug.
- Enhanced bioavailability of the drug at a specific site in the right proportion for a prolonged period.
- It improves the serum solubility of poorly water soluble drugs and also multiple drugs can be delivered to the same cell for combined synergetic therapy.

III. Application of Nanoparticles in Drug Delivery: Gaps and Concerns

A. Toxicity Evidence

Despite of potential benefits of nanoparticles in target drug delivery, results from *in vivo* studies have shown that nanoparticles can cause inflammation, lung cancer, mitochondrial damage, uptake through olfactory epithelium, platelet aggregation and cardiovascular effect. Studies have also shown that the nanoparticles by themselves are extremely potent, killing lymphoma cells without any additional drugs because of their ability to modulate cholesterol homeostasis, to regulate equilibrium within the lymphoma cells.

Cationic nanoparticles including gold and polystyrene have been shown to cause hemolysis and blood clotting, while usually anionic particles are quite non-toxic. Jong *et al.* (4) observed combustion originated and model nanoparticles can gain access to the blood following inhalation or instillation and can enhance experimental thrombosis. Radomski *et al.* (18) found that carbon derived nanomaterials (both single and multi-wall carbon nanotubes) induce platelet aggregation. High concentrations of anionic nanoparticles and cationic nanoparticles were toxic for the blood brain barrier. Investigations carried out by Sayes *et al.* (24) and Shvedova *et al.* (26) showed high doses of single wall carbon nanotubes induces reactive oxygen species generation, lipid peroxidation, oxidative stress, mitochondrial dysfunction, and changes in cell morphology in keratinocytes and bronchial epithelial cells. Oxidative stress has been implicated in the pathogenesis of neurodegenerative diseases such as Parkinson's and Alzheimer's diseases.

Fullerenes are being explored as potential new antimicrobial agents in view of their potential for induction of reactive oxygen species after photoexcitation. However, this may have an impact on microbial communities if they are released into the environment. Lovric *et al.* (11) showed "naked" quantum dots to be cytotoxic by induction of reactive oxygen species resulting in damage to plasma membranes, mitochondria and nucleus. SiO_2 exposure resulted in an increased reactive oxygen species levels and reduced glutathione levels indicating an increase in oxidative stress. Also Chang *et al.* found silica nanoparticles to be toxic at high dosages as shown by a reduction in cell viability / cell proliferation and by lactate dehydrogenase (LDH) release from the cells indicating membrane damage.

B. Knowledge Gaps in Environmental, Health and Safety Issues

Despite concerns of health and safety risks associated with engineered nanoparticles, there is a significant lack of quantitative analysis and empirical data on risk assessments and nanotoxicology. Much of this is due to scientific uncertainty over long-term medical reactions, and due to demonstrations that immune system failures due to the presence of nanoparticles distort empirical data for analyzing whether the nanoparticles are toxic. Other various reports also stress that further data on the risk assessments of toxicity and human health is essential before any nanomedicine products hit the market, since a greater concern is raised from the spread of free nanoparticles in the environment rather than individual exposure.

Absorbed species may also influence the potential toxicity of the inhaled particles. For nanoparticles, the situation is different as their size opens the potential for crossing the various biological barriers within the body. From a positive viewpoint, especially the potential to cross the blood brain barrier may open new ways for drug delivery into the brain. In addition, the nanosize also allows for access into the cell and various cellular organelles including the nucleus. Jong *et al.* (4) highlights besides the potential benefits attention should also drawn to the question how we should proceed with the safety evaluation of the nanoparticle formulations for drug delivery.

In order to harness full potential of nanotechnology in nanomedicine, adequate attention is needed to address safety and toxicological issues. For pharmaceuticals, specific drug delivery formulations may be used to increase the so called therapeutic ratio or index being the margin between the dose needed for clinical efficacy and the dose inducing adverse side effects. However, for these specific formulations a toxicological evaluation is needed. This is particularly true for the applications of nanoparticles for drug delivery.

Garber (6) observed an increasing concern among scientists and nanoethicists about how nanoparticles might affect or interfere with the biochemical pathways and processes of the human body. In addition, attention has been paid by the International Risk Governance Council on safety issues of handling and disposal of nanoparticles. Oberdorser *et al.* (15) point outs nanoparticle's behaviour is often unpredictable: they may behave differently *in vivo* than *in vitro*, may disintegrate into even smaller particles that are even more toxic, or cluster together in dangerous groups. Toxic accumulation in tissues or genetic mutations resulting from the use of nanodrugs or the implementation of any nanoparticles, nanodevices, or nanomaterials would not appear at the normal length of a clinical trial. Resnik (22) argues that small number of human test subjects in phase I clinical trials cannot adequately detect rare side effects that may affect susceptible subpopulations.

The Blood Brain Barrier (BBB) is well-known as the best gatekeeper in the body toward exogenous substances. Generally pharmaceuticals including most small molecules do not cross the BBB. Nevertheless, nanoparticles can cross the BBB and it may cause irreversible damage to brain cells as the nanoparticles are highly reactive and its behavior *in vivo* is unpredictable.

IV. Chitosan Nanoparticles for Target Drug Delivery Addressing Environment, Health and Safety Issues

Chitosan has received widespread attention in drug delivery systems due to their unique properties such as hydrophilicity, biocompatibility, biodegradability and mucoadhesivity.

Chitosan, a natural based polymer and its derivatives are good drug carriers because it can be readily modified due to presence of a primary amine group. Chitosan nanoparticles are drug carriers with wide development potential and it has advantage of slow / controlled drug release, which improves drug solubility and stability, enhances efficacy with reduced toxicity. It is a copolymer containing β-(1,4)-2-acetamido-D-glucose and β-(1,4)-2-amino-D-glucose. Chitosan is produced by removing an acetate moiety from chitin through hydration in concentrated alkali and this process is known as the deacetylation. Chitosan is soluble in most diluted acids. Under acidic conditions, chitosan can be dissolved in water after amino protonation to confer positive charges, gelation, and membrane-forming properties. The glycosidic bond of chitosan is hemiacetal, and thus is not stable in acid and will be hydrolyzed under acidic conditions, resulting in decreased viscosity and molecular weight of chitosan. Physical and chemical properties of chitosan depend mainly on its molecular weight and degree of deacetylation. As a natural product, chitosan is a renewable pharmaceutic adjuvant with good biocompatibility. Chitosan and its derivatives have strong potential for application as drug carriers. Wang *et al.* (31) observed chitosan itself has antitumor effect. Chitosan can act on tumor cells directly to interfere with cell metabolism, inhibit cell growth, or induce cell apoptosis. Chitosan molecule can be combined with glycoprotein in mucus to form hydrogen bonds resulting an adhesive effect.

Grafting cancer-specific ligands onto the chitosan nanoparticles has been successfully achieved as active targeting. Chitosan-conjugated components also respond to external or internal physical and chemical stimulus in targeted tumors. As a new drug delivery system, chitosan nanoparticles have attracted increasing attention for their wide applications in loading protein drugs, gene drugs, and anticancer chemical drugs, and via various routes of administration including oral, nasal, intravenous, and ocular.

V. Patent Trends in Relation to Chitosan Nanoparticles Technology

Patent information is important for researchers, inventors, technopreneurs, patent attorneys, public and private sector orgnaizations in avoiding duplicating research, patent infringements, patentability of inventions, valuation of intellectual property, due diligence on innovative activities and future research directions. Therefore, patent data was analyzed in relation to application of chitosan nanoparticles with an emphasis on medical applications.

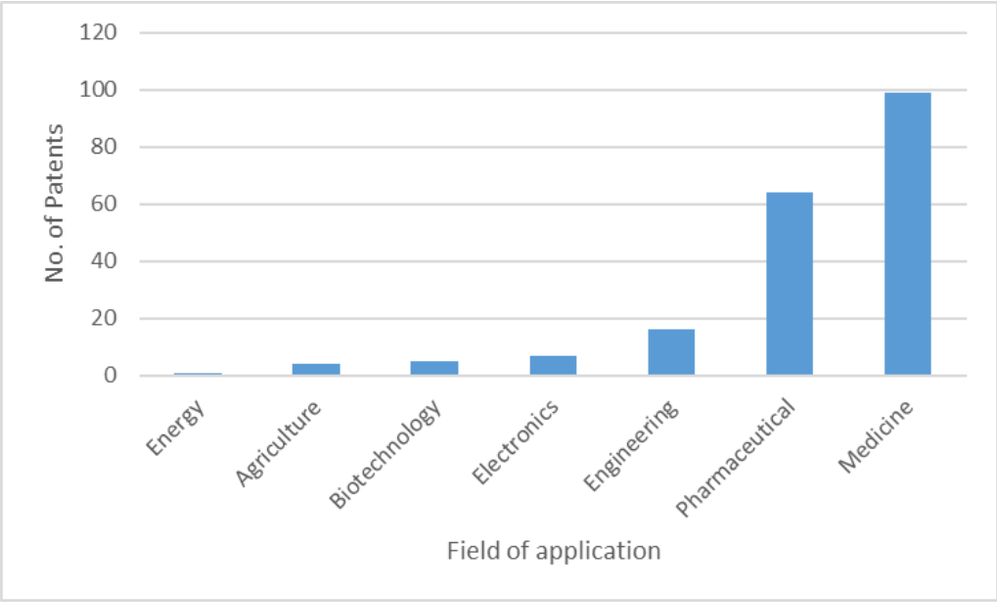

Fig. 1: Trends in Patent Filing on Applications of Chitosan Nanoparticles by Field of Application Since 1999

Fig. 1 depicts the patent distribution on the basis of field of application of chitosan nanoparticles. According to the represented analysis, chitosan nanoparticles are most commonly used in nanomedicine. Extensive research is being carried on application of nanoparticles in disease diagnosing, treating, and preventing. *In vitro* studies using nanoparticles have shown promising results especially in medical imaging, nanoscale surgery, tissue engineering, and the creation of alternative drug delivery systems. The patent trends depicted in the above graph corroborate with the extensive research in progress in the field of medicine. Nevertheless, it is evident from the graph that more research is yet to be done in relation to application of nanoparticles for betterment of the agriculture even though scientists have predicted that there is a great potential for chitosan nanoparticles to be used in the field of agricultural for sustainable food security.

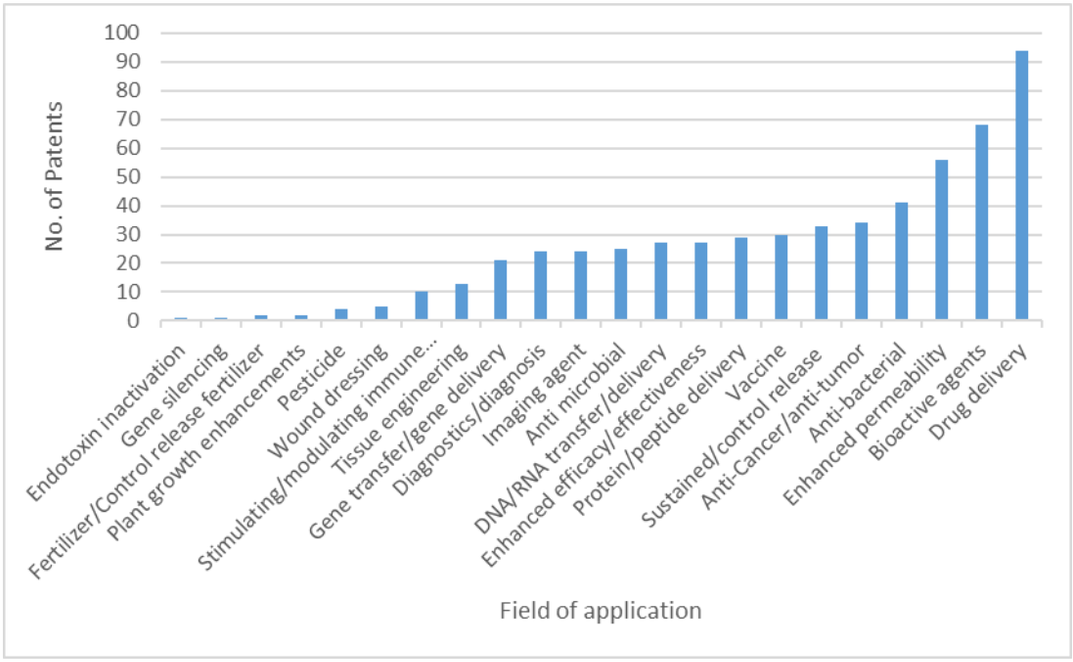

Fig. 2: Patent Distribution on the Basis of Various Applications of Chitosan Nanoparticles in Nanomedicine Since 1999

Fig. 2 represents the patent distribution according to different applications of chitosan nanoparticles in the field of nanomedicine. As evident from the graph, use of chitosan nanoparticles in drug delivery is the highest as chitosan nanoparticles are biocompatible, biodegradable, mucoadhesive and non-toxic. Accordingly, more innovations can be expected in use of chitosan nanoparticles in medicine in future. This will be an interesting message to investors who seek investing in early stages of Intellectual Property.

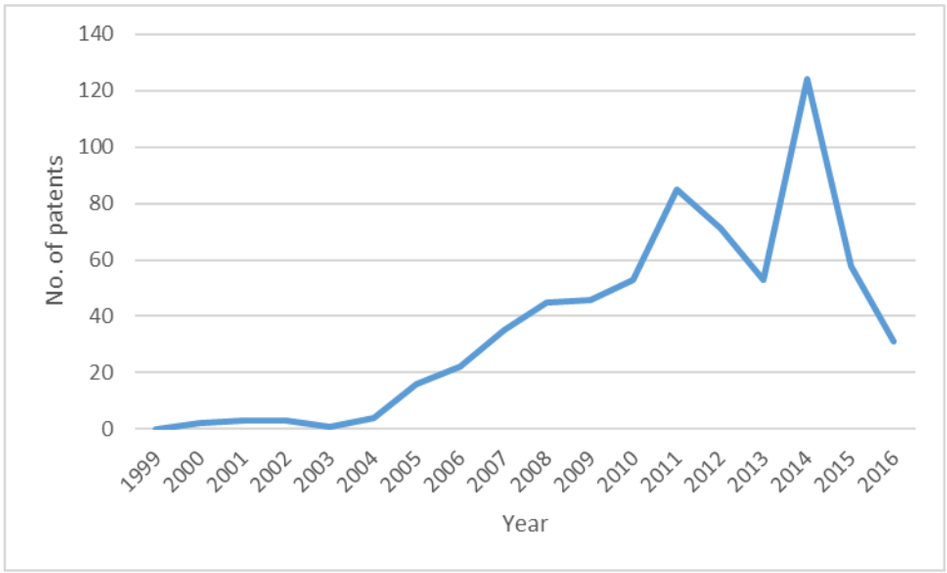

Fig. 3: Trends in Patent Filing on Applications of Chitosan Nanoparticles in Nanomedicine by Year

Fig. 3 shows the patent filing trend on application of chitosan nanoparticles in the field of nanomedicine. The exponential growth in patent filing suggests increasing research in application of chitosan nanoparticles and high probability of breakthrough innovation in the field of nanomedicine. The graph shows a decline in patenting in years 2015 and 2016. Once an inventor files a patent application, the patenting process takes some time to grant a patent. Patent examiners in the relevant receiving office carry out a thorough patent search at international level for patentability prior to grant the patent.

Accordingly, actual number of patents granted for years 2015 and 2016 would be higher than respective numbers depicted in the above graph.

VI. Conclusions and Recommendations

Since there is a knowledge gap in risk assessment quantitatively, further full risk assessment and quantitative empirical studies are required before either embark on clinical trials or commercialization of nanomedicine products. The primary goals of research towards nanoparticle mediated drug delivery should be more specific drug targeting and delivery, reduction in toxicity while maintaining therapeutic effects, greater safety and biocompatibility, and development of new safe medicines.

An ideal drug carrier should be recognized by the target cells specifically and selectively and must maintain the specificity of the surface ligands. The drug ligand complex should be stable in plasma and other bio-fluids. The drug carrier used should be non-toxic, nonimmunogenic and biodegradable. After recognition, the carrier system should release the drug moiety inside the target organs, tissues or cells. Nevertheless, chitosan can be improved further in terms of mechanical properties and biocompatibility before it becomes an ideal biomaterial for biomedical and tissue engineering applications. Chitosan nanoparticles can be used for target drug delivery studies as it is biocompatible, biodegradable and non-toxic. However, increasing charge density can induce and strengthen toxicity of chitosan. The chitosan has hemostatic characteristic and intravenous injection of excessive chitosan may cause death due to blood coagulation. Chitosan also has ant-microbial properties and therefore, studies are needed to ascertain the effect of chitosan nanoparticles on useful microbes in human body.

The main criteria in the search for appropriate carriers as drug delivery systems and designing new materials should be drug incorporation and release, stability and shelf life, biocompatibility, biodistribution, targeting and functionality. In addition, when used solely as carrier, the possible adverse effects of residual material after the drug delivery should also be considered. In this respect biodegradable nanoparticles with a limited life span as long as therapeutically needed would be ideal.

When designing drugs, mechanisms are hypothesized on release of drugs at the specific site. There is tendency to govern functionalities of drug carriers by pH *in vivo* and practically the drug carrier may not reach the intended target or even drug release will not take place as hypothesized due to diverse environment at the cellular level. Nanoparticles have qualitatively different physicochemical characteristics from micron-sized particles, which may result in changed body distribution, passage of the blood brain barrier, and triggering of blood coagulation pathways. In view of these characteristics, specific emphasis should be drawn on investigations in pharmacokinetics of nanoparticles. Uptake of drug carrier by cells or organelles can be size dependent. For example, an organelle will uptake 40-50 nm particles than the particles of 10 nm. Coupling specific proteins such as antibodies to the nanoparticle surface may enable a more specific immunologically directed targeting of the particles.

Although current tests procedures and protocols in drug and device evaluation may be appropriate to detect many risks associated with the use of these nanoparticles, it cannot be assumed that these assays will detect all potential risks in which additional assays may be needed. Toxicological studies have shown that some of the nanoparticles tend to accumulate in certain organs or tissues. Potential toxicity of a drug and nanoparticle carrier cannot be discriminated. Therefore, there should be a specific emphasis on the toxicity of the non-drug loaded particles especially when non-degradable particles are used for drug delivery. *In-vivo* toxicological studies have more focused on concentration or the dose level of nano carriers. But limited investigations are carried on morphology dependent toxicity. Therefore, more work to be done to ascertain whether morphology has any toxic effect. More information on toxicological risks needs to be provided before development of quantum dots with minimal risks. Researchers and scientists should question within themselves whether current regulations are robust enough to handle risks of nanomaterials when deal with a growing set of materials of which properties are largely unknown and nanodrugs reach market in an unprecedented manner. Therefore, mechanisms and protocols to screen such product should be in place before entering to the market. The capacity to carry our test trials (HR and infrastructure) in compliance with international standards will be needed. Patent examiners generally lacked expertise and training with respect to the emerging fields of nanotechnology and nanomedicine which can be a detriment to prompt commercialization of nanomedicine products in future.

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