ISSN: 0975-8585

Research Journal of Pharmaceutical, Biological and Chemical Sciences

Nanotechnologies and Nanoparticles in Pharmaceutical Sciences.

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ABSTRACT

Development of nanoparticles and nanotechnologies are currently one of the most active research fields worldwide. Several industrialized countries are making it a strategic priority for sustainable technological, economic and societal development. Nanoparticles provide massive advantages regarding drug targeting, delivery and release and, with their additional potential to combine diagnosis and therapy, emerge as one of the major tools in nanomedicine. In this regard these reviews elaborate the methods of nanotechnologies and types of nanoparticles with their features and future challenges with opportunities. Moreover, in future nanoparticles only provide many diseased as well as much more applications in the world without doubt.

Keywords: Nanotechnologies; nanoparticles; nanomedicine; drug delivery system; drug targeting.

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ISSN: 0975-8585

THE RESEARCH HISTORY

A study published in 2002 concluded that, from 1989 to 1998, the rate of increase of scientific publications on nanomaterials increased annually by 27%. This data indicated that over 30 countries were involved in research in this field, the most active being the United States, Japan, China, France, Great Britain and Russia, which accounted for 70% of publications. Also in 2002, Holister concluded that 455 private companies and 271 academic institutions and government entities were already involved in researching short-term applications in nanotechnology around the world. Since then, this field has continued to grow. Over the past twenty five years, many countries have developed strategic plans and decided to invest massively in nanotechnology research.

Worldwide research efforts are currently estimated at over US$8 billion for the year 2005 alone, about 40% of which would come from the private sector. A detailed review of international investments was carried out by Waters (2003) and by the European Commission (2004a). In 2003, the Japanese government invested the equivalent of US$800 million in the nanotechnology field, while the private sector invested an additional $830 million. The British Department of Trade and Industry reported, in 2002, that the first 1 One thousand billion or one million million carbon nanotube and fullerene production plants were under construction in Japan.

The European Union's 6th Framework Program, known as Nanoforum, allocated US$1.44 billion for the 2002-2006 period and is seeking to develop a European research and communications network integrating all aspects of nanotechnology, ranging from business to science and information intended for the general public. In May 2004, the Commission adopted a plan in which it proposed a safe, integrated and responsible European strategy.

Among the most active European countries are Germany, Great Britain, France, Switzerland, Belgium and the Netherlands. Other European countries are also active in nanotechnology R&D, but their investments are more limited: Ireland, Luxembourg, Italy, Austria, Denmark, Finland, Sweden and Norway.

INTRODUCTION

Nanoparticles exploit biological pathway to achieve payload delivery to cellular and intracellular targets. The targeting schemes explored for many of the reported nanoparticles systems suggest the great potential of targeted delivery to revolutionize cancer treatment (1). Nanotechnology has achieved the status as one of the vital research endeavors of 21st century, which may be called as "Nano-Century" with nanotechnology making its presence felt in different spheres of lives (2). Nanoparticles are at the cutting edge of the rapidly developing area of nanotechnology. Nanoparticles are small colloidal particles that are made non biodegradable and biodegradable polymers, and their diameter is around 200nm (3). The drug is dissolved, entrapped, encapsulated or attached to nanoparticles matrics (4). It may also offer a plenty of advantages over conventional dosage forms, which include improved efficacy, reduced toxicity, enhanced biodistribution and improved patient compliance.

The current definition defines nanoparticles as "particles with at least one dimension smaller than 100 nm or 0.1 µm, and with different properties than particles of larger diameters made of the same material" (5).

Nanoparticles have shown their specific accumulation in the inflamed tissues in the colon. The accumulation phenomenon of nanoparticles is observed to be particle size dependent with an increased adhesiveness for smaller particle diameters, which may therefore allow a selective delivery to the site of inflammation for the treatment of IBD. Indeed, nanoparticles showed promising results and demonstrated their therapeutic potential.

Nanoparticles in Drug Delivery

Nanoparticles are the versatile drug delivery system that can overcome physiological barriers and target drugs to the specific site. Nanoparticles can be used therapeutically as drug carriers, either by dissolving, entrapping or encapsulating the active substance (drug or biologically active materials) or by adsorbing or

attaching the active substances. The use of biodegradable polymers for nanoparticles preparation was preferable for this application to prevent complications with long-term deposition of nanoparticles or any residual component inside the ulcerated tissue (6). For colonic pathologies, it was shown that nanoparticles tend to accumulate at the site of inflammation in Inflammatory Bowel Disease (IBD). This is because in case of colitis, a strong cellular immune response occurs in the inflamed region (7).

Nanoparticle classification

Nanoparticles are generally classified based on their dimensionality, morphology, composition, uniformity, and agglomeration. An important additional distinction should be made between nanostructured thin films or other fixed nanometer-scale objects (such as the circuits within computer microprocessors) and free nanoparticles. The motion of free nanoparticles is not constrained, and they can easily be released into the environment leading to human exposure that may pose a serious health risk.It is also very important to recognize that not all nanoparticles are toxic; toxicity depends on at least chemical composition and shape in addition to simply size and particle ageing. In fact, many types of nanoparticles seem to be non-toxic (8-9) others can be rendered non-toxic (10), while others appear to have beneficial health effects (11-12).

Dimensionality

As shape or morphology of nanoparticles plays an important role in their toxicity, it is useful to classify them based on their number of dimensions. This is a generalization of the concept of aspect ratio.

1D nanomaterials. Materials with one dimension in the nanometer scale are typically thin films or surface coatings, and include the circuitry of computer chips and the antireflection and hard coatings on eyeglasses. Thin films have been developed and used for decades in various fields, such as electronics, chemistry, and engineering. Thin films can be deposited by various methods (13) and can be grown controllably to be only one atom thick, a so-called monolayer.

2D nanomaterials. Two-dimensional nanomaterials have two dimensions in the nanometer scale. These include 2D nanostructured films, with nanostructures firmly attached to a substrate, or nanopore filters used for small particle separation and filtration. Free particles with a large aspect ratio, with dimensions in the nanoscale range, are also considered 2D nanomaterials. Asbestos fibers are an example of 2D nanoparticles.

3D nanomaterials. Materials that are nanoscaled in all three dimensions are considered 3D nanomaterials. These include thin films deposited under conditions that generate atomic-scale porosity, colloids, and free nanoparticles with various morphologies.

Nanoparticle morphology

Morphological characteristics to be taken into account are: flatness, sphericity, and aspect ratio. A general classification exists between high- and low-aspect ratio particles. High aspect ratio nanoparticles include nanotubes and nanowires, with various shapes, such as helices, zigzags, belts, or perhaps nanowires with diameter that varies with length. Small-aspect ratio morphologies include spherical, oval, cubic, prism, helical, or pillar. Collections of many particles exist as powders, suspension, or colloids.

Nanoparticle composition

Nanoparticles can be composed of a single constituent material or be a composite of several materials. The nanoparticles found in nature are often agglomerations of materials with various compositions, while pure single-composition materials can be easily synthesized today by a variety of methods.

Nanoparticle uniformity and agglomeration

Based on their chemistry and electro-magnetic properties, nanoparticles can exist as dispersed aerosols, as suspensions/colloids, or in an agglomerate state. Hence, it is evident that nanoparticle agglomeration, size and surface reactivity, along with shape and size, must be taken into account when deciding considering health and environmental regulation of new materials.

NANOCRYSTALS AND NANOSUSPENSION

Nanocrystals are aggregates of around hundreds or thousands of molecules that combine in a crystalline form, composed of pure drug with only a thin coating comprised of surfactant or combination of surfactants. Problems typical of poorly soluble drugs like reduced bioavailability, improper absorption pattern and problems of preparing the parenteral dosage form may be resolved by formulation as nanocrystals. Nanoparticles offer the potential for targeting the mucosa of the gastrointestinal tract after oral administration, and targeting the cells of the mononuclear phagocytic system (MPS) to treat infections of the MPS such as fungal mycobacterial infections and leishmaniasis, thus serving as a favourable delivery system for drugs like amphotericin B, tacrolimus, etc. The size of nanocrystals allows for safe and effective passage through capillaries.

SOLID LIPID NANOPARTICLES

Solid lipid nanoparticles (SLN) were developed at the beginning of the 1990s as an alternative carrier system to emulsions, liposomes and polymeric nanoparticles as a colloidal carrier system for controlled drug delivery. Main reason for their development is the combination of advantages from different carriers systems like liposomes and polmeric nanoparticles. SLN have been developed and investigated for parenteral, pulmonary and dermal application routes.

Solid Lipid Nanoparticles consist of a solid lipid matrix, where the drug is normally incorporated, with an average diameter below 1µm. To avoid aggregation and to stabilize the dispersion, different surfactants are used that have an accepted GRAS (Generally Recognized as Safe) status. Nanoparticles are also produced by high pressure homogenisation as described for nanosuspensions. SLN have been considered as new transfection agents using cationic lipids for the matrix lipid composition. Cationic SLN for gene transfer can be formulated using the same cationic lipids as for liposomal transfection agents.

POLYMERIC NANOPARTICLES

Suspensions polymeric nanoparticles (SPNPs) consist of a biodegradable polymer. Biocompatibility is an essential feature for potential application as tissue engineering, drug and gene delivery and for new vaccination strategies. Most biodegradable polymers consists of synthetic polyesters like polycyanoacrylate or poly (D, L-lactide) and related polymers like poly (lactid acid) PLA or poly (lactide-co-glycolide) to give a few examples. Latest developments also include natural polymers like chitosan, gelatin, and sodium alginate to overcome some toxicological problems with the synthetic polymers. Polymeric nanoparticles represent a significant improvement over traditional oral and intravenous methods of administration in terms of efficiency and effectiveness.

The advantages of using SPNPs in drug delivery are many, being the most important that they generally increase the stability of any volatile pharmaceutical agents and that they are easily and cheaply fabricated in large quantities by a multitude of methods. Also, polymeric nanoparticles may have engineered specificity, allowing them to deliver a higher concentration of pharmaceutical agent to a desired location.

VARIOUS TECHNOLOGIES APPLIED FOR PREPARATION OF NANOPARTICLES

There are several methods for creating nanoparticles, including both attrition, pyrolysis and hydrothermal synthesis. In attrition, macro- or micro-scale particles are ground in a ball mill, a planetary ball mill, or other size-reducing mechanism. The resulting particles are air classified to recover nanoparticles.

Chemical Reactions

In order to produce Chemical reactions, like polymerizations, are one way to nanocrystalline dispersions, a milling chamber is charged produce nanoparticles; however they are normally not used with milling media (e.g. zirconium dioxide beads, silicium for the production of drug nanoparticles consisting of pure nitride beads, polystyrene beads), aqueous stabilizer / API. The moving milling these techniques are commercially very important e.g. for media causes high shear forces and thus attrition of the drug the

ISSN: 0975-8585

production of pharmaceutical coating materials in the particles. For large scale production, the mill can be run in form of latex dispersions. Currently there are five products on the market using this technology; many others are still in development.

Bottom-up Approaches

Bottom-up approaches start with drug molecules in solution. The first technology that was developed based drug molecules start to precipitate in larger formations. In this on HPH with a piston-gap homogenizer is a process classical precipitation process; the poorly soluble API is performed in aqueous media at room temperature. The homogenization step, a coarse suspension is forced through a precipitation is induced by mixing the drug solution with a very tiny homogenization gap. The particle size reduction is aqueous phase. This is often referred to as the "solvent / mainly caused by cavitations forces, shear forces, and particle anti solvent" approach. One approach was already developed collision. Later, this principle was further development in the 1980's by Sucker and colleagues. The principle of process, which can be also performed in water-reduced and classical precipitation, has been then further developed by non-aqueous media. To preserve the particle size, known as Evaporative Precipitation into Aqueous Solution stabilization (EPAS) with phospholipids or other surfactants.

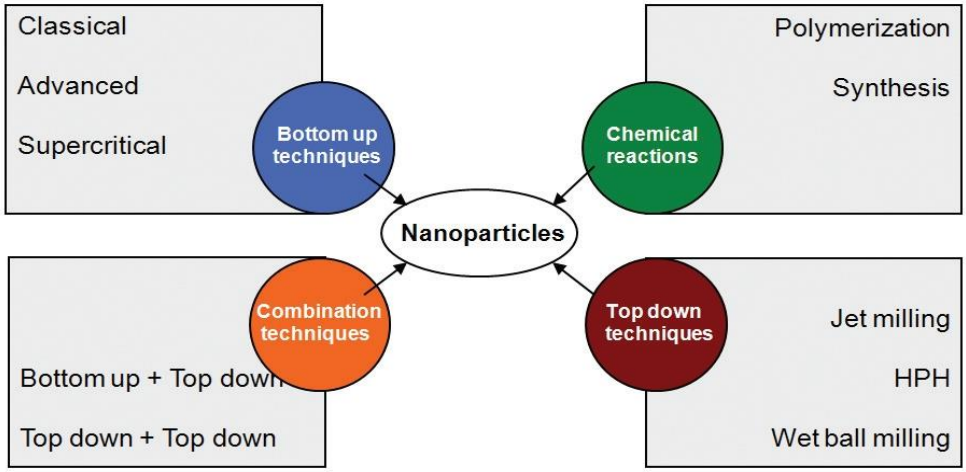

Figure 1: Overview of various principles to produce nanoparticles

Top-down Approaches

In contrast to the bottom-up technologies, one can also start in a way the preparation of nanoparticles can be with large API particles and break them down to small drug classified as nanoparticles. Therefore, this process type is regarded as top- down technology. Currently particle size reductions by these methods are common (14).

Dispersion of preformed polymers:

It is the most common technique used to prepare biodegradable nanoparticles. Supercritical fluids are environmentally safe (15) nanoparticles from poly (lactic acid) (PLA); poly (D, L A supercritical fluid can be generally defined as a solvent at a glycolide), PLG; poly (D, L-lactide-co-glycolide) (PLGA) temperature above its critical temperature, at which the fluid and poly (cyanoacrylates) (PCA) remains a single phase regardless of pressure. Supercritical CO2 (SC CO2) is the most widely used supercritical fluid because of its mild critical conditions, nontoxicity, non-flammability and low price (16).

Solvent evaporation method:

Organic solvents such as dichloromethane, chloroform or ethyl acetate are used to dissolve the polymer which is also used as the solvent for most common processing techniques involving supercritical dissolving the hydrophobic drug. The drug dissolved or fluids are supercritical anti-solvent (SAS) and rapid

dispersed in polymer solution is then emulsified in an expansion of critical solution. For preparation of the solute is insoluble in the supercritical fluid, the extract of small uniform sized particle size, High-speed homogenizer or the liquid solvent by supercritical fluid leads to the ultrasonication may be employed (17) instantaneous precipitation of the solute, resulting the formation of nanoparticles.

Spontaneous emulsification or solvent diffusion method:

This is a modification of solvent evaporation eventually precipitates. This technique is clean because precipitate is basically solvent free. This technique involves the use of water miscible and its modified solvent along with a small amount of the water immiscible process have been used for the product of polymeric organic solvent as an oil phase. An interfacial turbulence is generated between the two phases due to spontaneous diffusion of immiscible solvents leading to the formation of nanoparticles (18-19). Supercritical fluid technology technique, although environmentally friendly and suitable for mass production, requires specially designed equipment.

Polymerization method:

In this method, monomers are polymerized to form nanoparticles in an aqueous solution in the in vivo distribution of the nanoparticles. Drug may also be incorporated by adsorption onto the nanoparticles after polymerization completed. This performance technique has been reported for making polybutylcyanoacrylate or polyalkylcyanoacrylate.

A) Dispersion of preformed polymers by

1. Solvent evaporation method
2. Spontaneous emulsification or solvent diffusion method

B) Polymerization of monomers

Coacervation or ionic gelation method:

The method involves a mixture of two aqueous phases, of which one is the polymer Chitosan, a di-block co-polymer ethylene oxide or propylene oxide (PEO-PPO) and the other is a polyanion sodium tripolyphosphate. The major application of nanoparticles is in drug release and drug targeting. It has been found that particle size affects the drug release. Smaller particles offer larger surface area. In this method, positively charged amino group of Chitosan interacts with negative charged tripolyphosphate to form coacervates with a size in the range of nanometer. As a result, most of the drug loaded onto them will be exposed to the particle surface leading to fast drug release. On the contrary, drugs slowly diffuse inside larger particle. Coacervates are formed as a result of drawback; smaller particles tend to aggregate during storage electrostatic interaction between two aqueous phases, and transportation of nanoparticle dispersion. Hence, there is a compromise between a small size and maximum stability of nanoparticles.

Supercritical fluid technology:

Other methods such as organic phase separation methods require the use of wetting templates (20) have also been described in the enormous amounts of organic solvents which are hazardous to the environment as well as to human being. Therefore, the supercritical fluid technology is used.

CHARACTERIZATION OF NANOPARTICLES

Nanoparticles are generally characterized by their size, morphology and surface charge. Aqueous microscopic techniques as scanning electron microscopy phase(SEM) (21), transmission electron microscopy (TEM) and atomic force microscopy (AFM).

Dynamic light scattering (DLS)

Currently, the fastest and most popular method of determining particle size is photon-correlation spectroscopy imaging of delicate biological and polymeric nano and (PCS) or dynamic light scattering (DLS). DLS is widely used to determine the size of Brownian nanoparticles in colloidal description of size and size distribution and requires no suspensions in the nano and submicron ranges.

Atomic force microscopy (AFM)

AFM technique provides real picture which helps understand particles in Brownian motion causes a Doppler shift when the effect of various biological conditions (22). Moreover, particle size obtained by monochromatic light (laser) onto a solution of spherical light hits the moving particle, changing the wavelength of the incoming light.

Photon correlation spectroscopy (PCS)

It is possible to extract the size distribution and give a description of the particle's motion in the medium. The nature and intensity of the surface charge of nanoparticles are very important as it determines their interaction with the biological environment as well as their electrostatic interaction with bioactive compounds. The photon correlation spectroscopy (PCS) represents the most frequently used colloidal stability is analyzed through zeta potential of technique for accurate estimation of the particle size and size nanoparticles. This potential is an indirect measure of the distribution based on DLS (23).

PHARMACEUTICAL APPLICATIONS OF NANOTECHNOLOGY AND NANOPARTICLES

A key area in drug delivery is the accurately targeting of the drug to cells or tissue of choice. Drug targeting systems should be able to control the fate of a drug entering the body. Today's delivery technologies are far away from the design of the so called "magic bullet", proposed by Paul Ehrlich at the beginning of the 20th century, in which the drug is precisely targeted to the exact site of action. Nanotechnology offers here another challenge to come to this goal a bit closer, to deliver the drug in the right place at the right time (24). Nanotechnology is expected to bring a fundamental change in manufacturing in the next few years and will have an enormous impact on Life Sciences, including drug delivery, diagnostics, nutriceuticals and the production of biomaterials. To address this issue, multilayered nanoparticles can be engineered, where each layer will contain one drug from the cocktail, and their release will be sequenced in accordance with the appropriate timing of the delivery of each drug for combination therapy. Currently a significant amount of research shows that combination therapy is more effective than traditional therapies. Nanoparticles can be used in targeted drug delivery at the site of disease to improve the uptake of poorly soluble drugs, the targeting of drugs to a specific site, and drug bioavailability. Several anti-cancer drugs including paclitaxel, doxorubicin, 5-fluorouracil and dexamethasone have been successfully formulated using nanomaterials. Polylactic/glycolic acid (PLGA) and polylactic acid (PLA) based nanoparticles have been formulated to encapsulate dexamethasone, a glucocorticoid with an intracellular site of action. Dexamethasone is a chemotherapeutic agent that has anti-proliferative and anti-inflammatory effects. The drug binds to the cytoplasmic receptors and the subsequent drug-receptor complex is transported to the nucleus resulting in the expression of certain genes that control cell proliferation (25).

Site-specific-targeted drug delivery is important in the therapeutic modulation of effective drug dose and disease control. Targeted encapsulated drug delivery using NPs is more effective for improved bioavailability, minimal side effects, decreased toxicity to other organs, and is less costly. NP-based drug delivery is feasible in hydrophobic and hydrophilic states through variable routes of administration, including oral, vascular, and inhalation. In drug delivery, several approaches are currently being tested for better site-specific delivery of an effective dose using liposomes, polymeric micelles, dendrimeres, ceramic NPs, iron oxide, proteins, covalent binding, adsorption, conjugation, and encapsulation methods (26).

FUTURE OPPORTUNITIES AND CHALLENGES

Nanoparticles and nanoformulations have already been applied as drug delivery systems with great success; and nanoparticulate drug delivery systems have still greater potential for many applications, including

anti tumour therapy, gene therapy, and AIDS therapy, radiotherapy, in the delivery of proteins, antibiotics, virostatics, and vaccines and as vesicles to pass the blood - brain barrier. Nanoparticles provide massive advantages regarding drug targeting, delivery and release and, with their additional potential to combine diagnosis and therapy, emerge as one of the major tools in nanomedicine. The main goals are to improve their stability in the biological environment, to mediate the bio-distribution of active compounds, improve drug loading, targeting, transport, release, and interaction with biological barriers. There are many technological challenges to be met, in developing unique techniques and as delivery systems/carrier.

CONCLUSION

Nanotechnologies and nanoparticles represent a promising and fast-growing field. Indeed, current technological developments in this field are attempting to take advantage of these unique properties. However, a major challenge remains since current knowledge concerning health risks in this field is very fragmentary. In the short term, it will be almost impossible to acquire adequate knowledge of the risk associated with every types of nanoparticle. Moreover, in future nanoparticles only provide many diseased as well as much more applications in world.

ACKNOWLEDGEMENT

Authors wish to thank Director, Dr. K. N. Modi Institute of Pharmaceutical Education & Research, Modinagar (UP), India, for extending Library and ICT facility for this project.

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