ABSTRACT

Nanotechnology is widely anticipated as one of the key technologies of the 21st century. "Industrial nanotechnology applications are far-reaching, spanning all science and engineering disciplines. One of the most promising nanotechnology fields is Nanopharmaceuticals. Because nanomaterials may enter the body through dermal exposure, inhalation, ingestion, or ocular contact, they lend themselves to innovative drug delivery systems. Pharmaceutical research, toxicology studies, formulation, and manufacture of pharmaceutical products require material characterization to ensure consistent drug safety and effectiveness. Nano sized objects can be transformed in numerous ways to alter their characteristics. drug molecules sized in nano meter range provide some unique characteristics which leads to improve efficacy of drug. nanopharmaceuticals used such as liposome, nanotube, nanogel, dendrimers, polymeric nanoparticles.

KEYWORDS: Nanoparticles, Nanotube, Nanocrystal, Nanocarrier system.

INTRODUCTION

Nanotechnology involves the engineering of functional systems at the molecular scale. Such systems are characterized by unique physical, optical and electronic features that are attractive for disciplines ranging from materials science to biomedicine. One of the most active research areas of nanotechnology is nanomedicine, which applies nanotechnology to highly specific medical interventions for the prevention, diagnosis and treatment of diseases[1,2]. The surge in nanomedicine research during the past few decades is now translating into considerable commercialization efforts around the globe, with many products on the market and a growing number in the pipeline. Currently, nanomedicine is dominated
by drug delivery systems, accounting for more than 75% of total sales.\[^{[3]}\] Nanoparticles (NPs) containing encapsulated, dispersed, absorbed or conjugated drugs have unique characteristics that can lead to enhanced performance in a variety of dosage forms. When formulated correctly, drug particles are resistant to settling and can have higher saturation solubility, rapid dissolution and enhanced adhesion to biological surfaces, thereby providing rapid onset of therapeutic action and improved bioavailability. Nanotechnology could be strategically implemented in new developing drug delivery systems that can expand drug markets. Such a plan would be applied to drugs selected for full-scale development based on their safety and efficacy data, but which fail to reach clinical development because of poor biopharmacological properties, for example, poor solubility or poor permeability across the intestinal epithelium, situations that translate into poor bioavailability and undesirable pharmacokinetic properties.\[^{[4]}\]

**ADVANTAGES**

1. Improving the stability of hydrophobic drugs, rendering them suitable for administration
2. Improving bio distribution and pharmacokinetics, resulting in improved efficacy
3. Reducing adverse effects as a consequence of favored accumulation at target sites
4. Decreasing toxicity by using biocompatible nanomaterials.

**Various nanopharmaceuticals used as drug delivery system**

**Nanoparticles**

For better development of the nanoparticulate systems, it is essential to understand the pharmaceutically relevant properties of nanoparticles.\[^{[1-4]}\] There is significant interest in recent years in developing nanoparticles as a drug/gene delivery system. Nanoparticles are colloidal particles that range in size from 10 to 1000 nm in diameter, and are formulated using biodegradable polymers 5-10 in which a therapeutic agent can be entrapped, adsorbed, or chemically coupled. Nanoparticle formulation offers several advantages including elimination of toxicity because of cremophor, a solvent used in the previous formulation, and improved efficacy due to the greater dose of the drug that can be administered and delivered.

**Table-1 Types of nanoparticle**

<table>
<thead>
<tr>
<th>Serial no</th>
<th>Nanoparticle</th>
<th>Example of nanoparticle</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Nanotubes</td>
<td>Carbon</td>
</tr>
<tr>
<td>2</td>
<td>Nanowires</td>
<td>semiconductors, oxides</td>
</tr>
<tr>
<td>3</td>
<td>Nanocrystals</td>
<td>metals, magnetic materials</td>
</tr>
</tbody>
</table>
NANOTUBE
Carbon nanotubes are allotropes of carbon with a cylindrical nanostructure. Nanotubes have been constructed with length-to-diameter ratio of up to 132,000,000:1, which is significantly larger than any other material. These cylindrical carbon molecules have novel properties which make them potentially useful in many applications in nanotechnology, electronics, optics, and other fields of materials science, as well as potential uses in architectural fields. They may also have applications in the construction of body armor. They exhibit extraordinary strength and unique electrical properties, and are efficient thermal conductors. Nanotubes are members of the fullerene structural family, which also includes the spherical bucky balls. The ends of a nanotube may be capped with a hemisphere of the bucky ball structure. Their name is derived from their size, since the diameter of a nanotube is on the order of a few nanometers (approximately 1/50,000th of the width of a human hair), while they can be up to 18 centimeters in length (as of 2010). Nanotubes are categorized as single-walled nanotubes (SWNTs) and multi-walled nanotubes (MWNTs). Chemical bonding in nanotubes is described by applied quantum chemistry, specifically, orbital hybridization. The chemical bonding of nanotubes is composed entirely of sp2 bonds, similar to those of graphite. These bonds, which are stronger than the sp3 bonds found in diamonds, provide nanotubules with their unique strength. Moreover, nanotubes naturally align themselves into "ropes" held together by Van der Waals forces.[5]

NANOWIRE
A nanowire is a nanostructure, with the diameter of the order of a nanometer (10⁻⁹ meters). Alternatively, nanowires can be defined as structures that have a thickness or diameter constrained to tens of nanometers or less and an unconstrained length.

NANOCRYSTALS
Now a day many drug exhibit such a low solubility that micronization does not leads sufficiently high bioavailability and so the next step was taken to move from micronization to nanocrystals. drug nanocrystals are nanoparticles being composed of 100% drug without any matrix material that means the nanocrystal as its own carrier. By definition drug nanocrystal is crystalline particle with at least one dimension measuring less than 1000 nm, where 1 nm is defined as 1 thousand millionth of a meter[10⁻⁹][6]. nanocrystals particles have increase surface area particles which increase dissolution area and stabilized to prevent agglomeration.
Nanosuspension
A pharmaceutical nanosuspension is defined as very finely dispersed solid drug particles in an aqueous vehicle for either oral and topical use or parenteral and pulmonary administration. The particle size distribution of the solid particles in nanosuspensions is usually less than one micron with an average particle size ranging between 200 and 600 nm. Nanosuspensions differ from nanoparticles. Nanoparticles are commonly polymeric colloidal carriers of drugs whereas solid lipid nanoparticles are lipidic carriers of drugs. In nanosuspension technology, the drug is maintained in the required crystalline state with reduced particle size (i.e. increase in the surface area) leading to an increased dissolution rate and therefore improved bioavailability. Nano sized particles can increase solution velocity and saturation solubility because of the vapor pressure effect. In addition, the diffusional distance on the surface of drug nanoparticles is decreased, thus leading to an increased concentration gradient result to a much more pronounced increase in the dissolution velocity as compared to a micronized product. The stability of the particles obtained in the nanosuspension is attributed to their uniform particle size which is created by various manufacturing processes. The absence of particles with large differences in their size in nanosuspensions prevents the existence of different saturation solubilities and concentration gradients, consequently preventing the Ostwald ripening effect. Ostwald ripening is responsible for crystal growth and subsequently formation of microparticles. It is caused by a difference in dissolution pressure/saturation solubility between small and large particles. Molecules diffuse from the higher concentration area around small particles which have higher saturation solubility to an area around larger particles possessing a lower drug concentration. This leads to the formation of a
supersaturated solution around the large particles and consequently to drug crystallization and growth of the large particles.\[^7\]

Table 2 Nanosuspension formation technologies.\[^8\]

<table>
<thead>
<tr>
<th>Drug</th>
<th>Technology used</th>
<th>Advantages</th>
<th>Disadvantages</th>
</tr>
</thead>
<tbody>
<tr>
<td>Griseofulvin</td>
<td>Precipitation</td>
<td>-Simple process</td>
<td>Growing of drug crystals needs to be limit by surfactant addition</td>
</tr>
<tr>
<td></td>
<td></td>
<td>-Low cost equipment</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>-Ease of scale up</td>
<td></td>
</tr>
<tr>
<td>Naproxen</td>
<td>Media milling</td>
<td>-Little batch to batch variation</td>
<td>Require milling process for hours to days</td>
</tr>
<tr>
<td></td>
<td></td>
<td>-High flexibility in handling</td>
<td></td>
</tr>
<tr>
<td>Fenofibrate</td>
<td>High pressure Homogenization</td>
<td>-Aseptic production possible</td>
<td>High number of homogenization cycles</td>
</tr>
<tr>
<td></td>
<td></td>
<td>-Low risk of product contamination</td>
<td>-Prerequisite for drug to be in micronized state and suspension formation before homogenization</td>
</tr>
</tbody>
</table>

Nanogel

The term ‘nanogels’ defined as the nanosized particles formed by physically or chemically crosslinked polymer networks that is swell in a good solvent. The term “nanogel” (NanoGe\(^{TM}\)) was first introduced to define cross-linked bifunctional networks of a polion and a nonionic polymer for delivery of polynucleotides (cross-linked polyethyleneimine (PEI) and poly (ethylene glycol) (PEG) or PEG-cl-PEI) (Kabanov and Vinogradov, 2008). Sudden outbreak in the field of nanotechnology have introduced the need for developing nanogel systems which proven their potential to deliver drugs in controlled, sustained and targetable manner. With the emerging field of polymer sciences it has now become inevitable to prepare smart nano-systems which can prove effective for treatment as well as clinical trials progress.\[^9\]

Nanogels are superior drug delivery system than others

Because

1. The particle size and surface properties can be manipulated to avoid rapid clearance by Phagocytic cells, allowing both passive and active drug targeting Controlled and sustained drug release at the target site, improving the therapeutic efficacy and reducing side effects. Drug loading is relatively high and may be achieved without chemical reactions; this is an important factor for preserving the drug activity.
3. Ability to reach the smallest capillary vessels, due to their tiny volume, and to penetrate the tissues either through the paracellular or the transcellular pathways \[10\]

4. Highly biocompatible and biodegradable.

**Fig 2 drug release from nanogel**

**Nanocarrier used as drug delivery system**

A nanocarrier is nanomaterial being used as a transport module for another substance, such as a drug. Commonly used nanocarriers include micelles, polymers, carbon-based materials, liposomes and other substances.\[11\] Nanocarriers are currently being studied for their use in drug delivery and their unique characteristics demonstrate potential use in chemotherapy.

**Characterization**

Nanocarriers range from sizes of diameter 1–100 nm.\[12\] Because of their small size, nanocarriers can deliver drugs to otherwise inaccessible sites around the body. Since nanocarriers are so small, it is oftentimes difficult to provide large drug doses using them. The emulsion techniques used to make nanocarriers also often result in low drug loading and drug encapsulation, providing a difficulty for the clinical use.\[11\]

**Types**

Nanocarriers discovered thus far include polymer conjugates, polymeric nanoparticles, lipid-based carriers, dendrimers, carbon nanotubes, and gold nanoparticles. Lipid-based carriers include both liposomes and micelles. Examples of gold nanoparticles are gold nanoshells and nanocages.\[12\] Different types of nanomaterial being used in nanocarriers allows for hydrophobic and hydrophilic drugs to be delivered throughout the body.\[13\] Since
the human body contains mostly water, the ability to deliver hydrophobic drugs effectively in humans is a major therapeutic benefit of nanocarriers.\textsuperscript{[14]} Micelles are able to contain either hydrophilic or hydrophobic drugs depending on the orientation of the phospholipid molecules.\textsuperscript{[15,16]} Some nanocarriers contain nanotube arrays allowing them to contain both hydrophobic and hydrophilic drugs.\textsuperscript{[17]}

One potential problem with nanocarriers is unwanted toxicity from the type of nanomaterial being used. Inorganic nanomaterial can also be toxic to the human body if it accumulates in certain cell organelles.\textsuperscript{[18]} New research is being conducted to invent more effective, safer nanocarriers. Protein based nanocarriers show promise for use therapeutically since they occur naturally, and generally demonstrate less cytotoxicity than synthetic molecules.\textsuperscript{[19]}

**Targeted drug delivery system**

These are useful in the drug delivery process because they can deliver drugs to site-specific targets, allowing drugs to be delivered in certain organs or cells but not in others. Site-specificity is a major therapeutic benefit since it prevents drugs from being delivered to the wrong places.\textsuperscript{[13,15,16,17]} Nanocarriers show promise for use in chemotherapy because they can help decrease the adverse, broader-scale toxicity of chemotherapy on healthy, fast growing cells around the body. Since chemotherapy drugs can be extremely toxic to human cells, it is important that they are delivered to the tumor without being released into other parts of the body.\textsuperscript{[11,13,15,16]} Four methods in which nanocarriers can deliver drugs include passive targeting, active targeting, pH specificity, and temperature specificity.

**Passive targeting**

Passive targeting refers to a nanocarrier's ability to travel down a tumor's vascular system, become trapped, and accumulate in the tumor. This accumulation is caused by the enhanced permeability and retention effect \textsuperscript{[11, 16, 20]} which refers to the poly(ethylene oxide) (PEO) coating on the outside of many nanocarriers. PEO allows nanocarriers to travel through the leaky vasculature of a tumor, where they are unable to escape. The leaky vasculature of a tumor is the network of blood vessels that form in a tumor, which contain many small pores. These pores allow nanocarriers in, but also contain many bends that allow the nanocarriers to become trapped. As more nanocarriers become trapped, the drug accumulates at the tumor site.\textsuperscript{[20]} This accumulation cause large doses of the drug to be delivered directly to the tumor site.\textsuperscript{[11]} PEO may also have some adverse affects on cell-nanocarrier interactions, weakening
the effects of the drug, since many nanocarriers must be incorporated into the cells before the
drugs can be released.\cite{20}

**Active targeting**

Active targeting involves the incorporation of targeting modules such as ligands or antibodies on the surface of nanocarriers that are specific to certain types of cells around the body. Nanocarriers have such a high surface-area to volume ratio allowing for multiple ligands to be incorporated on their surfaces.\cite{12} These targeting modules allow for the nanocarriers to be incorporated directly inside of cells, but also have some drawbacks. Ligands may cause nanocarriers to become slightly more toxic due to non-specific binding, and positive charges on ligands may decrease drug delivery efficiency once inside of cells.\cite{16,20} Active targeting has been shown to help overcome multi-drug resistance in tumor cells.\cite{21}

**Uses**

Most of research on nanocarriers is being applied to their potential use in drug delivery, especially in chemotherapy. Since nanocarriers can be used to specifically target the small pores, lower pH’s, and higher temperatures of tumors, they have the potential to lower the toxicity of many chemotherapy drugs.\cite{11,13,15,16} Also, since almost 75% of anticancer drugs are hydrophobic, and therefore demonstrate difficulty in delivery inside human cells, the use of micelles to stabilize, and effectively mask the hydrophobic nature of hydrophobic drugs provides new possibilities for hydrophobic anticancer drugs.\cite{14}

**Liposomal drug delivery system:** Liposomes are a form of vesicles that consist either of many, few or just one phospholipid bilayers. The polar character of the liposomal core enables polar drug molecules to be encapsulated. Amphiphilic and lipophilic molecules are solubilized within the phospholipid bilayer according to their affinity towards the phospholipids. Participation of nonionic surfactants instead of phospholipids in the bilayer formation results in niosomes. Channel proteins can be incorporated without loss of their activity within the hydrophobic domain of vesicle membranes, acting as a size-selective filter, only allowing passive diffusion of small solutes such as ions, nutrients and antibiotics. Thus, drugs that are encapsulated in a nanocage functionalized with channel proteins are effectively protected from premature degradation by proteolytic enzymes. The drug molecule, however, is able to diffuse through the channel, driven by the concentration difference between the interior and the exterior of the nanocage. Liposomes have the distinct advantages of being
both nontoxic and biodegradable because they are composed of naturally occurring substances. Biologically active materials encapsulated within liposomes are protected to varying extent from immediate dilution or degradation, suggesting drug carrier systems for the transport of drugs and other bioactive capsules to disease-affected organs. The unique ability of liposomes to entrap drugs both in an aqueous and a lipid phase make such delivery systems attractive for hydrophilic and hydrophobic drugs. Because of advancements in the methods of preparing and formulating liposomes, high-entrapment efficiencies are possible for incorporating drugs into liposomes, creating a tremendous pharmaceutical impact. Furthermore, such encapsulation has been shown to reduce drug toxicity while retaining or improving the therapeutic efficacy. Several laboratories have reported the use of liposomes as drug carriers in the treatment of cancer, leishmaniasis, metabolic disorders, and fungal diseases. Innovative research in liposomal drugs has led to commercialization of several anticancer therapeutics such as Doxil, Myocet, two liposome-based anticancer drugs; doxorubicin; and an antifungal drug formulation, AmBisome, which is a liposomal formulation of amphotericin B used for systemic therapy. Liposomes may have a use in gene delivery to correct gene-associated disorders or for vaccine therapy. A quantitative entrapment of DNA can be achieved using the preparation of empty liposomes with cationic lipids followed by mixing with DNA or a plasmid of interest. Because of its convenience and efficacy, cationic lipid mediated gene delivery technology is a promising system for in vivo gene therapy. Clinical trials of large-size lipid–DNA complexes have mostly shown a lack of adverse effects and moderate expression in a relatively low fraction of cells, but no decisive clinical disadvantages.

**Liposomes For Gene Delivery:** It is important to dissect the overall cell uptake process into individual steps. In fact different studies have indicated that successful gene transfer in vitro involves:

1) The packaging of DNA,
2) The adhesion of packaged DNA to the cell surface,
3) internalization of DNA,
4) escape of DNA from endosomes if endocytosis is involved,
5) DNA expression in cell nuclei.

To perform all of the above steps, liposomes have been explored as a delivery system for DNA as early as in 1979. The encapsulation of plasmid DNA into liposomes and the
introduction of poliovirus RNA and SV40 DNA into cells via liposomes\cite{29,30} were reported between 1979 and 1980.

**Drug properties and Liposome association**

**Table 3** Lipid-based nanoparticles for Drug Delivery

<table>
<thead>
<tr>
<th>Hydrophilic</th>
<th>Retained in aqueous interior It may be difficult to get high loading</th>
<th>Slowly released over several hours- several days</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hydrophobic</td>
<td>Inserted into hydrophobic interior of the liposome bilayer it can disrupt liposome at high concentrations</td>
<td>Excellent retention</td>
</tr>
</tbody>
</table>

**Dendrimer**: Dendrimers are a new class of polymeric materials. A dendrimer is typically symmetrical around the core and often adopts a spherical three dimensional architecture that provides a high degree of surface functionality and versatility. Dendrimers are repeatedly branched macromolecules or nano-sized, radially symmetric molecules with well defined, homogeneous and monodisperse structure consisting of tree-like arms or branches. The name comes from the Greek word Dendron which translates to tree. Dendrimers are globular or spheroid nanostructures that are engineered to encapsulate the molecules into their interior void spaces or to attach onto the surface.\cite{31} Shape, size, and reactivity are determined by interior branching, surface functionalities, generation (shells) and chemical composition of the core. Dendrimers are constructed through a set of repeating chemical synthesis procedures that build up from the molecular level to the nanoscale region under conditions that are easily performed in a standard organic chemistry laboratory. The dendrimer diameter increases linearly where as the number of surface groups increases geometrically. Dendrimers are very uniform with extremely low polydispersities, and are generally created with dimensions incrementally grown in approximate nanometer steps from 1 to over 10nm. The control over size, shape and surface functionality makes dendrimers one of the commercially available smartest nanotechnologies.\cite{32} Divergent synthesis was the first introduced method for the production of dendrimers by Vogtle in 1978.

**Table 1: Properties Of Dendrimer And Linear Polymers**\cite{33,34,35,36,37}

<table>
<thead>
<tr>
<th>Property</th>
<th>Dendrimers</th>
<th>Linear Polymers</th>
</tr>
</thead>
<tbody>
<tr>
<td>Structure</td>
<td>Compact and Globular</td>
<td>Not compact</td>
</tr>
<tr>
<td>Shape</td>
<td>Spherical</td>
<td>Random coil</td>
</tr>
<tr>
<td>Aqueous solubility</td>
<td>High</td>
<td>Low</td>
</tr>
<tr>
<td>Compressibility</td>
<td>Low</td>
<td>High</td>
</tr>
<tr>
<td>Polydispersity</td>
<td>Monodisperse</td>
<td>Polydisperse</td>
</tr>
<tr>
<td>Reactivity</td>
<td>High</td>
<td>Low</td>
</tr>
<tr>
<td>Structural control</td>
<td>Very high</td>
<td>Low</td>
</tr>
</tbody>
</table>
CONCLUSION

In the future, nanopharmaceuticals will alter the human body (on a nanoscale) in ways that we cannot now imagine but it is essential to consider benefits and side effects of the use of nanopharmaceuticals. In this review, we have tried to provide details of challenges that nanotechnology and nanomedicine face for the human health, in a number of cases highlighting the problems to be addressed. The development of engineered nanoparticles with substantial biomedical significance has posed new opportunities and challenges for pharmacology and therapeutics.

REFERENCES


