A REVIEW ON USE OF NANOTECHNOLOGY IN PHARMACEUTICALS

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ABSTRACT

Drug particles in the nanometer size range have unique characteristic that can lead to enhanced performance in a variety of dosage forms. Nature is the ultimate in nanotechnology producing nanostructures that offer function proteins and many others compounds. Nanotechnology is an industrial revolution based on integration of disciplines that could change every facets of human life. There are number of nanoparticle used as carrier for therapeutic and diagnostic agents namely polymeric nanoparticles, solid lipid nanoparticles, Nano suspension and nanocrystals, polymeric micelles, ceramic nanoparticles, liposomes, dendrimers, magnetic nanoparticles, nanoshells, nanowires, nonopores, quantum dots, ferro fluids. In this paper the main scientific and technical aspects of nanotechnology are introduced and some of its applications are discussed. Applications to medicine and physiology imply materials and devices designed to interact with the body at subcellular (i.e., molecular) scales with a high degree of specificity. This can potentially translate into targeted cellular and tissue specific clinical applications designed to achieve maximal therapeutic affects with minimal side effects. Nanotechnology and Nano engineering stand to produce significant scientific and technological advances in diverse fields including medicine and physiology.

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INTRODUCTION

Nanotechnology can be defined as the science and engineering involved in the design, synthesis, characterization, and application of materials and devices whose smallest functional organization in at least one dimension is on the nanometer scale or one billionth of a meter. At these scales, consideration of individual molecules and interacting groups of molecules in relation to the bulk macroscopic properties of the material or device becomes important, since it is control over the fundamental molecular structure that allows control over the macroscopic chemical and physical properties. Applications to medicine and physiology imply materials and devices designed to interact with the body at subcellular (i.e., molecular) scales with a high degree of specificity. This can potentially translate into targeted cellular and tissue specific clinical applications designed to achieve maximal therapeutic affects with minimal side effects. Nanotechnology and Nano engineering stand to produce significant scientific and technological advances in diverse fields including medicine and physiology. In a broad sense, they can be defined as the science and engineering involved in the design, synthesis, characterization, and application of materials and devices whose smallest functional organization in at least one dimension is on the nanometer scale, ranging from a few to several hundred nanometers. A nanometer is one billionth of a meter or three orders of magnitude smaller than a micron, roughly the size scale of a molecule itself (e.g., a DNA molecule is about 2.5 nm long while a sodium atom is about 0.2 nm). To give an appreciation of just how significant an order of magnitude is, let alone three orders when going from micron to nanometer scales, consider that no one would ever walk from New York to San Diego, but with a single order of magnitude change in speed (the equivalent of changing speed from walking to driving), you would get to San Diego across the United States in about 2 days. Flying, which would be two orders of magnitude faster than walking, would get you across the United States in a few hours and in a supersonic plane (or three orders faster than walking), it would take you minutes. (Walking a straight line between the two cities would take about 42 days at an average speed of 3 miles per hour.)

The potential impact of nanotechnology stems directly from the spatial and temporal scales being considered: Materials and devices engineered at the nanometer scale imply controlled manipulation of individual constituent molecules and atoms in how they are arranged to form the bulk macroscopic substrate. This, in turn, means that Nano engineered substrates can be designed to exhibit very specific and controlled bulk chemical and physical properties as a result of the control over their molecular synthesis and assembly. For applications to medicine and physiology, these materials and devices can be designed to interact with cells and tissues at a molecular (i.e., subcellular) level with a high degree of functional specificity, thus allowing a degree of integration between technology and biological systems not previously attainable. It should be appreciated that nanotechnology is not in itself a single emerging scientific discipline but rather a meeting of traditional sciences such as chemistry, physics, materials science, and biology to bring together the required collective expertise needed to develop these novel technologies.

Nanotechnology in nature:

Nature has enough evidence of nanotechnology, based on its ability to work at the atomic, molecular and supramolecular levels. The mechanisms of the biological and physical world operate mainly at the range of 1 to 100 nm. The diameter of a hydrogen atom is about 0.1nm which is too small to be seen with human eyes. A molecule (such as water molecule) may be made up of 20 to 30 atoms and has a diameter of about 1nm. The width of a DNA molecule is about 2.5nm, a typical protein is between 1 to 20nm and ATP biochemical motor is 10 nm in diameter. The human hair is about 10, 000nm thick while human cells range from 5,000 to 200,000 nm in size. Although this is larger than Nano scale, the viruses that attack human cells fall within 10 to 200nm, which is within the nanometer region. Nature is the ultimate in nanotechnology, producing nanostructures that offer functional proteins and many other compounds at cellular level of great significance to life on earth. It is thought that one of the functions of proteins and compounds that exist at cellular level is that of Nano technological separations. Biological systems are thought by some scientists to have come about through a process of dynamic self assembly comprising separation and compartmentalization of many substances into the desired pattern or device. Some biological systems contain Nano systems that are devoted to specific functions such as locomotion, where actin moves along myosin and kinesin moves along microtubules. Thus a DNA molecule can be seen as a self-assembly machine which replicates itself and also produces complex organisms under the right conditions. Ribosomes construct protein molecules with precision following instructions from DNA.

Molecular motors that make up the human muscles are sophisticated Nano machines that can convert chemical energy to mechanical energy with high efficiency. Ribosomes, another molecule, can construct protein molecules with precision following instructions from DNA. Photosynthesis is carried out in green plants by cells of Nano size, which employ energy to synthesize organic compounds by using cheap raw materials they pick up.

The wonder of how a wall gecko is able to hang upside down is due to the millions of Nano hairs on each toe. Each hair grips the ceiling with a miniscule force. Moth’s eyes are antiglare and antireflective due to nano technology which helps to reduce easy predation on them while the colors on butterfly wings are due to light being bounced off Nano scale layers in the structure of the wings. Nature depicts how soluble molecules that are able to recognize and bind to specific materials can be used to shape and control the growth of crystals and other nanostructures. This can be typified by the way macromolecules govern self-assembly of bio minerals or the action of antifreeze proteins in slowing down the growth of ice crystals or promoting their nucleation.

Sufficient knowledge and insight into the principles of natural systems would enhance the design and fabrication of manmade nanostructures that may mimic the functions of natural systems. For instance, biomolecules such as proteins, peptides, DNA, lipids and carbohydrates can act as templates their shapes and chemical properties can be employed to arrange inorganic substances such as metals on Nano scale.
Table 1: Types of nanoparticles used as carrier for Therapeutic and diagnostic agents:

<table>
<thead>
<tr>
<th>Sr. No.</th>
<th>Type of Nanoparticles</th>
<th>Material Used</th>
<th>Applications</th>
</tr>
</thead>
<tbody>
<tr>
<td>A</td>
<td>Polymeric Nanoparticles</td>
<td>Biodegradable Polymers</td>
<td>Controlled and targeted drug delivery</td>
</tr>
<tr>
<td>B</td>
<td>Solid Lipid Nanoparticles</td>
<td>Melted lipid dispersed in an aqueous surfactant</td>
<td>Least toxic and more stable colloidal carrier systems as alternative materials to polymers</td>
</tr>
<tr>
<td>C</td>
<td>Nano suspensions &amp; Nano crystals</td>
<td>The drug powder is dispersed in a surfactant solution</td>
<td>Stable system for controlled delivery of poorly soluble drugs.</td>
</tr>
<tr>
<td>D</td>
<td>Polymeric micelles</td>
<td>Amphiphilic block copolymers</td>
<td>Systemic and controlled delivery of water-insoluble drugs</td>
</tr>
<tr>
<td>E</td>
<td>Liposomes</td>
<td>Phospholipid Vesicles</td>
<td>Controlled and targeted drug delivery</td>
</tr>
<tr>
<td>F</td>
<td>Dendrimers</td>
<td></td>
<td>Carriers for site specific drug delivery</td>
</tr>
<tr>
<td>G</td>
<td>Magnetic nanoparticles</td>
<td>An inorganic core of iron oxide (magnetite Fe2O3, maghemite or other insoluble ferrites) coated with polymer such as dextran.</td>
<td>Drug targeting, Diagnostic tool in biology and Medicine</td>
</tr>
<tr>
<td>H</td>
<td>Nano shells coated with Gold</td>
<td>Dielectric (typically gold sulfide or silica) core and a metal (gold) shell</td>
<td>Tumor Targeting</td>
</tr>
<tr>
<td>I</td>
<td>Quantum Dots</td>
<td>CdSe–CdS core-shell</td>
<td>Targeting, Imaging Agent</td>
</tr>
<tr>
<td>J</td>
<td>Ferro fluids</td>
<td>Iron oxide magnetic nanoparticles surrounded by a polymeric layer</td>
<td>For capturing cells and other biological targets from blood or Other fluid and tissue samples.</td>
</tr>
</tbody>
</table>

Polymeric Nanoparticles:

Polymeric nanoparticles are colloidal solid particles with a size range of 10 to 1000nm and they can be spherical, branched or shell structures. The first fabrication of nanoparticles was about 35 years ago as carriers for vaccines and cancer chemotherapeutics. They are developed from non-biodegradable and biodegradable polymers. Their small sizes enable them to penetrate capillaries and to be taken up by cells, thereby increasing the accumulation of drugs at target sites. Drugs are incorporated into nanoparticles by dissolution, entrapment, adsorption, attachment or by encapsulation, and the nanoparticles provide sustained release of the drugs for longer periods, e.g., days and weeks. Nanoparticles enhance immunization by prevention of degradation of the vaccine and increased uptake by immune cells. One of the determinants of the extent of uptake by immune cells is the type of polymer employed. In a study comparing...
Poly(caprolactone) (PCL), poly (lactide-co-glycolide) (PLGA) and their blend. PCL nanoparticles were the most efficiently taken up by immune cells due to their hydrophobicity. However, all polymeric nanoparticles elicited vaccine (diphtheria toxoid) specific serum IgG antibody response significantly higher than free diphtheria toxoid. To target drugs to site of action, the drug can be conjugated to a tissue or cell specific ligand or coupled to macromolecules that reach the target organs. To target an anticancer agent to the liver, polymeric conjugate nanoparticles which comprised biotin and diamine terminated poly (ethyleneglycol) with a galactose moiety from lactobionic acid were prepared. Some other applications of nanoparticles include possible recognition of vascular ultrastructures. A current application of nanoparticles carriers is the controlled release for tumors answer to treatment, because of the nonspecific side effects, topic administration for enhancement penetration and distribution in and across the skin barrier; and pH-sensitive nanoparticles to improve oral bioavailability of drugs such as cyclosporine A. Some polymers used in the fabrication of nanoparticles include chitosan, alginate, albumin, gelatin, polyacrylates, polycaprolactones, poly (D, L-lactide-co-glycolide) and poly (D, L-lactide) However, there are concerns about polymeric nanoparticles including cytotoxicity of by-products (although some, such as polyanhdyrides, degrade into products that are biocompatible) and scalability.

APPLICATIONS:

Corticoids release:

Corticoids are anti-inflammatory drugs with high efficiency in the treatment of posterior segment eye diseases such as uveitis. It has also been proved that corticoids can improve the wound healing and may be effective in the case of fibrosis (proliferative vitreoretinopathy and sub retinal neovascularization). Systemic administration of corticoids determines a series of side effects, topical administration being preferred. In the eventuality of topic administration, only a small amount of the drug reaches the posterior segment of the eye. Direct injections in the vitreous can increase the therapeutic efficiency but usually repeated injections are required, generating a great discomfort for the patient. Some risks are also associated with this technique, such as vitreous hemorrhage or retinal detachment. Some local toxic effects have been also observed. Another modality to insure a therapeutic concentration of the drug is to use drug releasing implants. There are also disadvantages associated with this technique: a large surgical incision is required to install the implant; the implant is very difficult to remove and it exists the possibility that the implant would migrate, endomaging the epithelium. An alternative to these rather complicated methods is to use corticoids loaded nanoparticles. Some of the most promising polymers are PLGA due to their very low toxicity. Gomez et al. presented the synthesis of dexamethasone loaded PLGA nanoparticles. Dexamethasone is a poorly soluble crystalline corticoid generally used in the treatment of diabetic macular edema (as an implantable device).

Anticancer therapies:

In the anticancer therapy, one of the worst problems is the low tumors answer to treatment, because of the nonspecific bioavailability of the administered anticancer agent. By using nanoparticles it is possible to achieve the bioaccumulation of the drug in the target tissue. In the most cases, the EPR (enhanced permeation and retention) effect is responsible for the accumulation of drug in the tumors tissue. Hapca et al. synthesized PLA nanoparticles on which they have grafted monoclonal antibodies with a high specificity for the treatment of ovarian cancer and lymphomas. A current application of nanoparticles carriers is the controlled release of heme oxygenase (HO-1) inhibitors. HO-1 is an enzyme involved in the oxidation of heme, by cleavage of the porphyrin ring leading to formation of biliverdin, carbon monoxide and free iron. Biliverdin is subsequently hydrogenated by the cytosolic enzyme biliverdin reductase to form bilirubin (a potent antioxidant). Although high levels of bilirubin in the blood can cause toxic effects to central nervous system, in a normal quantity, the bilirubin protects the human cells against oxidation. Tumors cells can also use HO-1 to protect themselves from oxidative processes. Especially the renal and prostatic tumors are characterized by a high concentration of HO-1.

These observations led to the hypothesis that the administration of a heme inhibitor could increase the tumor’s sensibility to oxidative processes. The oxidative processes can then be easily increased by certain usual drugs: cisplatin, anthracyclin, camtoptiocin etc. One of the most interesting inhibitor of HO-1 is the zinc protoporphyrin (ZnPP). Apart from inhibiting HO, ZnPP also induces cell death by a secondary mechanism. The protoporphyrin derivates are also known to be efficient photosensitzers. These derivatives absorb light in the UV- visible region and being excited to a long-lived triplet state can interact with molecular oxygen, which on becoming singlet oxygen exerts cytotoxic effect. The use of ZnPP is limited by its poor solubility in water. Macromolecular porphyrin compounds were also synthesized but the molecular weight was not high enough to allow the tumor targeting. A product with an adequate average molecular weight was obtained by Iyer et al., by conjugation of ZnPP with PEG. The ZnPP-PEG conjugate showed a good releasing kinetic for in vivo and in vitro models, accumulating in the target tissue – by EPR. The main disadvantage was represented by the poor loading capacity (only 1.5% weight of ZnPP). The increased amount of PEG induces a high viscosity even for a minimal loading with ZnPP. Because of the high viscosity, the parenteral administration it is not available. Another method to achieve the targeting of HO inhibitors is the synthesis of amphiphilic copolymers [poly(styrene-alt-maleic anhydride) (SAM)] that can load high amounts of ZnPP (up to 60%). Besides, the SAM copolymer proved to be biocompatible and it also has a stimulating effect for the immune system – by activating the macrophages (T and NK cells). Other drugs that have been successfully used in the treatment of cancer are paclitaxel and doxorubicin. In the case of paclitaxel, after the oral administration, the bioavailability is as low as 1%.
Paclitaxel is eliminated from bloodstream at the firsthepatic passage, by cytochrome P-450. By synthesizing small enough nanoparticles, it is possible to attach and maintain the nanoparticle paclitaxel complex to the intestinal mucosa until the complete absorption of paclitaxel to portal vein. The particles dimensions have an important role in their capacity to cross through biological membranes. Several studies confirmed that particles with a diameter of 5000 nm can reach the lymphatic circulatory system. Particles with a diameter lower than 500 nm can cross the epithelium membrane by endocytosis and nanoparticles with diameter lower than 50 nm can reach the interstitial spaces. These observations allowed the development of novel pharmaceuticals formulations for oral administration of anticancer drugs.

Blood-brain barrier:

It is known that between the blood streamline and the central nervous system there is a barrier known as the blood-brain barrier (BBB). BBB allows only the exchange of ions in order to maintain a constant osmotic pressure and the passage of nutrients. Its role is to protect the brain and the spinal axis from any chemical or bacteriological threats. The protection offered by the BBB comes at a certain price: it is impossible to get drugs through the barrier, so the therapy for the central nervous system is very difficult. In the brain, endothelial cells are packed more tightly together, due to the existence of tight zonulae occludentes junctions between them. The blood brain barrier recognizes therapeutic agents as foreign particles and doesn’t allow their passage. Because of the blood-brain barrier, finding a way to deliver bioactive substances to brain has become a real challenge. One of the methods to achieve drug delivery to the central nervous system is to entrap the drugs into nanoparticles. Because of their reduced size, nanoparticles are able to pass through the vascular endothelium of BBB. There are several studies that showed good result in the treatment of brain tumors by drug loaded nanoparticles.

Vaccines and gene therapy:

Another field where nanoparticles are very important is gene delivery. By encapsulating the genes into nanoparticles it is possible to protect them from degradation in the presence of certain factors (pH, bile, proteolytic enzymes). The entrapment of genes into nanoparticles has encountered some problems regarding the stability of the synthesized structures during the preparations as well as after administration. One method to ensure the stability is to bind the genes to the surface of nanoparticles or Nano capsules. The binding must be reversible in order to allow the cleavage of the complex once the target has been reached. In order to improve the biocompatibility of the product it is better to avoid the use of surfactants. A method to obtain nanoparticles without using a surfactant was proposed by Castadello et al. who obtained nanoparticles able to bind DNA without using a surfactant. The nanoparticles have a PMMA core and a shell of PEG and positively charged groups. The PEG chains are both biocompatible and biodegradable and provide a steric stability while the positively charged groups bind DNA. By using these complex structures, the risk of physical desorption is greatly decreased. Such a vaccine is also stable and non-toxic while it is possible to administer it orally.

Gene therapy is a potential method for treating neurodegenerative diseases such as Parkinson. The controlled delivery of genes responsible for GNDF (Glial Cell Line-Derived Neurotropic Factor) formation stops the disease evolution and maintains a constant level of dopamine despite cells lost because of the disease. Also the delivery of genes involved in the tyrosine hydroxylase has shown good results. Initially viral vectors were used (recombinant adenoviruses or retroviruses). A more efficient method is to entrap the genes into nanoparticles. One of the preferred polymers is poly(ethyleneimine). Polyethyleneimine (PEI) has been already used to deliver genes inside the neurons with promising results. It protects the DNA inside the nanoparticle while the ionic character favors the membrane penetration by binding to the negatively charged heparin sulphate, expressed on the cell surface.

Diagnostic:

Sun et al. presented the modality to obtain copper chlorophyll labeled nanoparticles. These nanoparticles can be directly traced in vivo by analytical electron microscopy (AEM). Nanoparticles covered with Polisorbate T-80 have been detected in the brain, what proves the existence of endocytosis and/or transcytosis at some extent. Therefore this type of nanoparticles can be used in the functional exploration of the brain.

Figure 2: Solid Lipid Nanoparticles.
Solid Lipid Nanoparticle (SLN):

Colloidal particles ranging in size between 10 and 1000 nm are known as nanoparticles. They are manufactured from synthetic/natural polymers and ideally suited to optimize drug delivery and reduce toxicity. Over the years, they have emerged as a variable substitute to liposomes as drug carriers. The successful implementation of nanoparticles for drug delivery depends on their ability to penetrate through various anatomical barriers, sustained release of their contents and their stability in the nanometer size. However, the scarcity of safe polymers with regulatory approval and their high cost have limited the wide spread application of nanoparticles to clinical medicine. To overcome these limitations of polymeric nanoparticles, lipids have been put forward as an alternative carrier, particularly for lipophilic pharmaceuticals. These lipid nanoparticles are known as solid lipid nanoparticles (SLNs), which are attracting wide attention of formulators world-wide. SLNs are colloidal carriers developed in the last decade as an alternative system to the existing traditional carriers (emulsions, liposomes and polymeric nanoparticles). They are a new generation of submicron sized lipid emulsions where the liquid lipid (oil) has been substituted by a solid lipid. SLN offer unique properties such as small size, large surface area, high drug loading and the interaction of phases at the interfaces, and are attractive for their potential to improve performance of pharmaceuticals, neutraceuticals and other materials. SLNs are attracting major attention as novel colloidal drug carrier for intravenous applications. The SLNs are submicron colloidal carrier which is composed of physiological lipid, dispersed in water or in an aqueous surfactant solution. So if systematically investigated, SLNs may open new vista in research and therapy.

Advantages and problems of SLNS and other nanoparticles:

SLNs combine the advantages and avoid the drawbacks of several colloidal carriers of its class. Potential disadvantages such as poor drug loading capacity, drug expulsion after polymeric transition during storage and relatively high water content of the dispersions (70-99.9%) have been observed. The drug loading capacity of conventional SLN is limited by the solubility of drug in the lipid melt, the structure of the lipid matrix and the polymeric state of the lipid matrix. If the lipid matrix consists of especially similar molecules (i.e. tristearin or tripalmitin), a perfect crystal with few imperfections is formed. Since incorporated drugs are located between fatty acid chains, between the lipid layers and also in crystal imperfections, a highly ordered crystal lattice cannot accommodate large amounts of drug. Therefore the use of more complex lipids is more sensible for higher drug loading.

Applications:

SLN for Parenteral Application:

Wissing et al. (2004) intensively reviewed parenteral use of SLN. SLN are very suitable for systemic delivery because they consist of physiologically well-tolerated ingredients and they have good storage capabilities after lyophilization and/or sterilization. When injected intravenously, SLN are sufficiently small to circulate in the micro vascular system and prevent macrophage uptake in case of hydrophilic coating. Therefore, SLN have been suggested for viral and non viral gene delivery. Cationic SLN has been demonstrated to bind genes directly via electrostatic interactions, and have potential benefits in targeted gene therapy in treatment of cancer. The charge of particles can also be modulated via the composition, thus allowing binding of oppositely charged molecules (Olbrich et al 2001; Tabatt et al; 2004; Pedersen et al 2006). Treatment of central nervous system diseases such as brain tumors, AIDS, neurological and psychiatric disorders is often constrained by the inability of potent drugs to pass blood brain barrier (BBB). Hydrophilic coating of colloids improves the transport of these through BBB and tissue distribution (Kreuter 2001; Wang et al., 2002). Fundaro et al, 2000, prepared doxorubicin loaded stealth and non-stealth SLN and observed that the stealth nanoparticles were present in blood at higher concentrations than non-stealth SLN after 24h following intravenous administration.

SLN for Nasal Application:

Nasal administration was a promising alternative noninvasive route of drug administration due to fast absorption and rapid onset of drug action, avoiding degradation of labile drugs (such as peptides and proteins) in the GI tract and insufficient transport across epithelial cell layers (Lee et al., 1994). In order to improve drug absorption through the nasal mucosa, approaches such as formulation development and prodrg derivatization have been employed. SLN has been proposed as alternative Tran’s mucosal delivery systems of macromolecular therapeutic agents and diagnostics by various research groups (Muller and Keck 2004; prego et al., 2005). In a recent report, coating polymeric nanoparticles with PEG gave promising results as vaccine carriers (Vila et al., 2004). The role of PEG coating of polyactic acid nanoparticles in improving the Trans mucosal transport of the encapsulated bioactive molecule reported to be successful by Tobio et al, 1998. This concept can be useful for solid lipid nanoparticles.

SLN for Respiratory Application:

The lungs offer a high surface area for drug absorption by avoiding first-pass effects. Rapid drug absorption by aerosolization of drugs (in the 1-3 μm size range) occurs since the walls of alveoli in the deep lung are extremely thin (Agu et al., 2001; Banga 2003). Lymphatic drainage plays an important role in the uptake of particulates in the respiratory system. SLN can be proposed as carriers of anti-cancer drugs in lung cancer treatment or peptide drugs to improve their bioavailability. Assessment of inhaled radio-labeled SLN bio distribution has been described and the data showed an important and significant uptake of the radio-labeled SLN into the lymphatic after inhalation (Videira et al., 2002). In a recent study, ant tubercular drugs (rifampicin, isoniazid and pyrazinamide) were incorporated into various formulations of solid lipid particles ranged from 1.1 to 2.1 μm and formulations were nebulized to guinea pigs by mouth for direct pulmonary delivery (Pandey et al., 2005a and 2005b). Nebulization of solid lipid particles carrying ant tubercular drugs was observed to be successful in improving drug bioavailability and reducing the dosing frequency for better management of pulmonary tuberculosis.
SLN for Ocular Application:
Ocular drug administration via SLN has been reported several times (Friedrich et al. 2005). Bio-compatibility and mucoadhesive properties of SLN improve their interaction with ocular mucosa and prolong corneal residence time of the drug, with the aim of ocular drug targeting. Cavalli et al. (2002) evaluated SLN as carriers for ocular delivery of tobramycin in rabbit eyes. As a result SLN significantly enhanced the drug bioavailability in the aqueous humor. Cavalli et al., (1995) also studied pilocarpine delivery via SLN, which is commonly used in glaucoma treatment, earlier. They reported very similar results in order to enhance the ocular bioavailability of drug.

SLN for Rectal Application:
A few reports are available on the rectal drug administration via SLN in the literature (Sznitowska et al., 2000). Sznitowska et al., 2001 incorporated diazepam into SLN for rectal administration in order to provide a rapid action. They applied SLN dispersions on rabbits and performed bioavailability studies. They found that lipid matrix which is solid at body temperature is not an advantageous system for diazepam rectal delivery. They decided to employ lipids which melt around body temperature in their next experiments. This area seems very open to investigation, especially when the benefits of rectal route are taken into consideration. PEG coating seems to be a promising approach on rectal delivery and consequently, enhancement of bioavailability.

SLN for Topical application:
SLN and NLC are very attractive colloidal carrier systems for skin applications due to their various desirable effects on skin besides the characteristics of a colloidal carrier system. They are well suited for use on damaged or inflamed skin because they are based on non-irritant and non-toxic lipids (Wissing and Muller 2003). Researchers have reported intensively on the topical application of SLN. During the last few years, SLN and NLC have been studied with active compounds such as Vitamin E (Dingler et al., 1999), tocopherol acetate (Wissing and Muller 2001), retinol (Jenning et al., 2000), ascorbyl palmitate (Uner et al., 2005a and 2005b), clotrimazole (Souto et al., 2004), triptolide (Mei et al., 2003), phophyllotoxin (Chen et al., 2006) and a nonsteroidal androgen RU 58841 (Munster et al., 2005) for topical application. A completely new, recently discovered area of application is the use of SLN in sun-protective creams (Waghmare et al., 2012).

SLN in Cancer chemotherapy:
From the last two decades several chemotherapeutic agents have been encapsulated in SLN and their in-vitro and in-vivo efficacy have been evaluated. Tamoxifen, anticancer drugs have been incorporate-rated in SLN to prolong the release of drug following i.v. administration in breast cancer (Murthy, 2005). Tumor targeting has been achieved with SLN loaded with drugs like methotrexa and camptotheclin. Metoxantrone SLN local injections were formulated to reduce the toxicity and improve the safety and bio efficacy of the drug in treating breast cancer and lymph node metastases (Wong et al., 2006).

Oral SLN in ant tubercular chemotherapy:
Antitubercular drugs such as rifampsin, isoniazid, and pyrazinamide-loaded SLN systems were able to reduce the dosing frequency and improve patient compliance. Antitubercular drugs loaded SLNs were prepared using solvent diffusion technique (Pandey et al., 2005).

SLN for potential agriculture application:
Essential oil extracted from Artemisia arborescens L. when incorporated in SLN, were able to reduce the rapid evaporation compared with emulsions and the systems have been used in agriculture as a suitable carrier of ecologically safe pesticide (Lai et al., 2006).

Nano suspension and Nano crystals:
Poorly water soluble drugs pose a great challenge in drug formulation development. The low saturatedsolubility and dissolution velocity lead to poorbioavailability. With the increasing number of newlydeveloped lipophilic drug compounds, manytechniques have been proposed, such as solid dispersions, co-solvents, emulsions, liposomes and nanoparticles based on lipidic or polymer carriers. However, the use of large amounts of excipients or organic solvents is limited in pharmaceutical formulations due to possible toxicity of the compounds. A pharmaceutical Nano suspension is defined as very finely dispersed solid drug particles in an aqueous vehicle for either oral or topical use or parenteral and pulmonary administration. The particle size distribution of the solid particles in Nano suspensions is usually less than one micron with an average particle size ranging between 200 and 600 nm Nano suspension is a sub-micron colloidal dispersion of drug particles which are stabilized by surfactants, polymers or a mixture of both. This formulation has a high drug loading, low incidence of side effects by the excipients, and low cost owing to the increased surface to volume ratio of the Nano crystals, an increase in saturated solubility and very fast dissolution rate can be seen, especially below particle sizes of 1µm. Nano suspensiontechnology can also be used for drugs, which are insoluble in both water and organic solvents. Hydrophobic drugs such as naproxen, bupravaquone, nimesulide, amphotericin B, omeprazole, nifedipine are formulated as Nano suspension. The stability of the particles obtained in the Nano suspension 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 Nano suspensions prevents the existence of different saturation solubility’s and concentration gradients, consequently preventing the Ostwald ripening effect.
Ostwald ripening is responsible for crystal growth and subsequently formation of micro particles. 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.

Applications:

Oral drug delivery:

The oral route is the preferred route for drug delivery because of its numerous well-known advantages. The efficacy performance of the orally administered drug generally depends on its solubility and absorption through the gastrointestinal tract. Hence, a drug candidate that exhibits poor aqueous solubility and/or dissolution rate limited absorption is believed to possess low and/or highly variable oral bioavailability. Owing to low oral bioavailability, such a drug candidate would have to be administered in larger excess than actually required if it were completely bioavailable in order to achieve a therapeutically active concentration, thus making the therapy costly. Orally administered antibiotics such as atovaquone and bupravaquone reflect this problem very well. Nanosizing of such drugs can lead to a dramatic increase in their oral absorption and subsequently bioavailability.

The amelioration in oral bioavailability can be attributed to the adhesiveness of the drug Nano suspension, increased surface area (due to reduction in particle size by 10–50-fold), and increased saturation solubility, leading to an increased concentration gradient between the gastrointestinal tract lumen and blood, and increased dissolution velocity. This enhancement in bioavailability will lead to a subsequent reduction in drug dose, rendering the therapy cost-effective and obliterating any undue drug dumping in the body. Some milestones Atovaquone, an antibiotic indicated for treating opportunistic Pneumocystis carinii infections in HIV patients, non-complicated P. falciparum malaria and leishmanial infections (Looaeresuwan et al. 1999), shows poor bioavailability (10–15%) because of its dissolution-rate limited absorption and has to be administered high doses (750 mg twice daily). Administration of atovaquone as a Nano suspension resulted in a 2.5-fold increase in oral bioavailability as compared to the commercial product Wellvone, which contains the micronized drug (Scho¨ ler et al. 2001). Danazol, a poorly bioavailable gonadotropin inhibitor, showed a drastic improvement in bioavailability when administered as a Nano suspension as compared to the commercial danazol macro suspension Danocrine (Liversidge & Cundy 1995). Danazol Nano suspension led to an absolute bioavailability of 82.3%, whereas the marketed danazol suspension Danocrine was 5.2% bioavailable. In addition, danazol Nano suspension resulted in a reduction in the intersubject variability and fed/fasted ratio of danazol. Amphotericin B, a highly effective polyene antibiotic used for systemic mycoses and leishmaniasis lacks oral bioavailability. However, oral administration of amphotericin B as a Nano suspension produced a substantial improvement in its oral absorption in comparison to orally administered conventional commercial formulations such as Fungizone, AmBisome and micronized amphotericin B (Kayser et al. 2003). Orally administered amphotericin B Nano suspension brought about a high uptake of Nano particulate drug through the gastrointestinal tract. This is reflected by the considerable reduction it brought about in the number of L. donovaniparasites in the liver of infected female Balb/c mice as compared to other commercial formulations.

Nano suspensions are also advantageous in achieving quick onset of action for drugs that are completely but slowly absorbed, i.e., those having high tmax values. This is illustrated by the study carried out for naproxen, a nonsteroidal anti-inflammatory drug. A dosage form with fast onset of action would be highly desirable for naproxen. A study involving a comparison of the pharmacokinetic profiles of naproxen in the form of Nano suspension, suspension (Naprosyn) and tablet (Anaprox) forms revealed that the time required to achieve Cmax was reduced by approximately 50% for the Nano suspension compared to the suspension and tablet. Additionally, naproxen Nano suspension resulted in a 2.5 to 4.5 fold increase in the AUCs during the first hour of the study (Liversidge & Conzentino 1995; Merisko-Liversidge et al. 2003). Numerous drug candidates that are poorly water-soluble are required to be taken over a prolonged period of time for effective medication. However, many of them cannot be formulated into sustained release dosage forms because of the risk of dose dumping and poor in-vivo performance. Although approaches such as a change in microenvironment and complexation with cyclodextrins have resulted in the successful incorporation of some poorly water-soluble drugs in sustained release dosage forms (Chowdhary et al. 2003), these solutions are not applicable to all poorly water-soluble drugs. Nano suspensions, on the other hand, enable incorporation of all hydrophobic drugs in well-established sustained-release technologies. However, while doing so, the effect and the interaction of dosage form excipients with the Nano crystalline drug must be critically investigated. Drug Nano suspensions can also be incorporated into dosage forms such as tablets, capsules and fast melts by means of standard manufacturing techniques. Ketoprofen Nano suspension has been successfully incorporated into pellets to release the drug over a period of 24 h (Remon et al. 2001). In spite of the tremendous potential of Nano suspensions in oral delivery, formulating compounds as Nano crystalline dispersions is not of value when metabolic and/or permeation-related issues affect bioavailability. However, in future, it should be possible to engineer Nano suspensions by using the agents that enhance permeation (Aungst 2000) and/or minimize gut-related metabolic issues (Kusuhara et al. 1998; Benet et al. 1999). This amalgamated approach would facilitate delivery of the compounds belonging to BCS Class IV that exhibit poor water solubility and poor membrane permeability.
Parenteral drug delivery:

The parenteral route is an invasive route. Parenteral administration of drugs is critical and often associated with the problems such as the limited number of acceptable excipients, restrictions on the quantities of excipients approved for parenteral use, the stringent requirements of the aseptic production process, safety issues, patient noncompliance and biological problems such as allergic reactions and thrombophlebitis. Despite all these limitations, the parenteral route still retains its value because of its special advantages, such as quick onset of action in case of emergency, reduction in dose of the drug and the ability to target the drug quickly to the desired site of action, especially in the case of severe infections. The parenteral route is often employed as an alternative when the drug is either not absorbed through the gastrointestinal tract or undergoes extensive first-pass metabolism. For administration by the parenteral route, the drug either has to be solubilized or have particle/globule size below 5µm to avoid the capillary blockade. The current approaches for parenteral delivery include salt formation, solubilization using co-solvents, micellar solutions (Kim et al 2001), complexation with cyclodextrins and recently liposomes (Dupont 2002). However, there are limitations on the use of these approaches because of limitations on their solubilization capacity and parenteral acceptability. In this regard, liposomes are much more tolerable and versatile in terms of parenteral delivery. However, they often suffer from problems such as physical instability, high manufacturing cost and difficulties in scale-up. Nano suspensions appear to be a unique approach to solving the problems mentioned above. From the formulation perspective, Nano suspensions meet almost all the requirements of an ideal drug delivery system for the parenteral route. Since the drug particles are directly Nano sized, it becomes easy to process almost all drugs for parenteral administration. Moreover, the absence of any harsh solvents/co-solvents and/or any potentially toxic ingredient in Nano suspensions enables them to bypass the limitations of parenteral administration attributed to conventional formulations strategies.

Hence, Nano suspensions enable significant improvement in the parent rally tolerable dose of the drug, leading to a reduction in the cost of the therapy and also improved therapeutic performance. The maximum tolerable dose of paclitaxel Nano suspension was found to be three times higher than the currently marketed Taxol, which uses Cremophore EL and ethanol to solubilize the drug. In the MV-522 human lung xenograft murine tumors model, paclitaxel Nano suspensions at doses of 90 and 100mg kg⁻¹ showed no cases of death (n=49) whereas Taxol at a concentration of 30mg kg⁻¹ showed a 22% death rate (Merisko-Liversidge et al 1996, 2003). Similarly, the Nano suspensions of other anticancer agents, such as etoposide and camptothecin, revealed an improvement in the tolerance level of the drug compared to the marketed preparations. In addition, Nano suspensions have been found to increase the efficacy of the parenterally administered drug (Merisko-Liversidge et al 2003). A comparison of the efficacy of paclitaxel Nano suspension with Taxol using the mammary 16-C murine tumors model (n=45 for each experimental group) revealed the superiority of paclitaxel Nano suspension over Taxol in reducing the median tumor burden (Merisko-Liversidge et al 2003). Similarly, aphidicolin, a poorly water-soluble new anti-parasitic lead molecule, when administered as Nano suspension revealed an improvement in EC50 from 200 to 40 ngmL⁻¹ in comparison to DMSO-dissolved drug (Kayser 2000). Recently, clofazimine, a poorly water-soluble anti leprotic drug, has been successfully formulated as a Nano suspension. Clofazamine Nano suspension revealed an improvement in stability and efficacy over the liposomal clofazimine in M. avium-infected female mice (Peters et al 2000). It is noteworthy that after intravenous administration of a Nano suspension, the drug nanoparticles are sequestered by mononuclear phagocytic system (MPS) cells and Kupffer cells, as observed in the case of various other colloidal drug carriers (Illum et al 1982; Juliano 1988; Toster et al 1990; Stolnik et al 1995; Neal et al 1998; Liu et al 2000; Moghimi et al 2001). The particles are recognized as being foreign bodies and are phagocytosed by the macrophages mainly in the liver (60–90%), spleen (approximately 1–5%) and to a very small extent in the lungs. Since this uptake by macrophage is a natural process, it is referred to as ‘natural targeting’ in the literature. Natural targeting does not affect the safety profile of the drug. In fact, it helps in increasing the drug tolerance as MPS cells or Kupffer cells can act as a controlled release vehicle for the drug, enabling its prolonged action (Martin et al 1982; Adachi et al 1992; Soma et al 2000). Sequestration by MPS is believed to be the reason for the increased efficacy of the antibiotics and anti infective Nano suspension form as they are naturally targeted to the macrophages that are the mainstays of various bacterial and fungal infections. Moreover, in order to achieve macrophage targeting in a rapid manner, the surface properties of Nano suspensions could be modulated in a controlled way to alter the plasma protein adsorption pattern. A multitude of factors, such as the physical properties of the drug particles, the dose, the infusion time, the intrinsic solubility of the drug in the hemodynamic pool of the blood, the drug– plasma protein interaction, the plasma protein interaction pattern and the phenomenon of natural targeting influence the bio distribution and pharmacokinetic profile of the Nano particulate drug after parenteral administration. Nano suspensions can be administered via different parenteral routes, ranging from intra-articular to intraperitoneal to intravenous injection. Currently, studies are in progress to identify strategies for manipulating the surface properties, size and shape of drug Nano suspensions in order to eliminate sequestration by the phagocytic cells of MPS-enriched organs whenever desired.
Ocular drug delivery:

Nano suspensions can prove to be a boon for drugs that exhibit poor solubility in lachrymal fluids. For delivery of such drugs, approaches such as suspensions and ointments have been recommended. Although suspensions offer advantages such as prolonged residence time in a cul-desac (which is desirable for most ocular diseases for effective treatment) and avoidance of the high tonicity created by water soluble drugs, their actual performance depends on the intrinsic solubility of the drug in lachrymal fluids. Thus, the intrinsic dissolution rate of the drug in lachrymal fluid governs its release and ocular bioavailability. However, the intrinsic dissolution rate of the drug will vary because of the constant inflow and outflow of lachrymal fluids. Hence, suspensions may fail to give consistent performance. However, Nano suspensions, by their inherent ability to improve the saturation solubility of the drug, represent an ideal approach for ocular delivery of hydrophobic drugs. Moreover, the Nano particulate nature of the drug allows its prolonged residence in the cul-de-sac, giving sustained release of the drug. To achieve sustained release of the drug for a stipulated time period, Nano suspensions can be incorporated in a suitable hydrogel base or mucoadhesive base or even in ocular inserts. An approach that has recently been investigated to achieve the desired duration of action of the drug is the formulation of polymeric Nano suspensions loaded with the drug. The bio erodible as well as water-soluble/ permeable polymers possessing ocular tolerability (Pignatello et al 2002) could be used to sustain the release of the medication. The Nano suspensions can be formulated using the quasi-emulsion and solvent diffusion method. The polymeric Nano suspensions of flurbiprofen and ibuprofen have been successfully formulated using acrylate polymers such as Eudragit RS 100 and Eudragit RL 100 (Bucolo et al 2002; Pignatello et al 2002). The polymeric Nano suspensions have been characterized for drug loading, particle size, zeta potential, in-vitro drug release, ocular tolerability and in-vivo biological performance. The designed polymeric Nano suspensions revealed superior in-vivo performance over the existing marketed formulations and could sustain drug release for 24 h. The scope of this strategy could be extended by using various polymers with ocular tolerability.

Pulmonary drug delivery:

Nano suspensions may prove to be an ideal approach for delivering drugs that exhibit poor solubility in pulmonary secretions. Currently such drugs are delivered as suspension aerosols or as dry powders by means of dry powder inhalers. The drugs used in suspension aerosols and dry powder inhalers are often jet milled and have particle sizes of microns. Because of the micro particulate nature and wide particle size distribution of the drug moiety present in suspension aerosols and dry powder inhalers, the following disadvantages are encountered:

- Limited diffusion and dissolution of the drug at the site of action because of its poor solubility and micro particulatenature, which may affect the bioavailability of the drug
- Rapid clearance of the drug from the lungs because of ciliary movements.
- Less residence time for the drugs, leading to absence of prolonged effect.
- Unwanted deposition of the drug particles in pharynx and mouth.

Nano suspensions can solve the problems associated with conventional systems because of their versatile nature. The Nano particulate nature of the drug allows the rapid diffusion and dissolution of the drug at the site of action. At the same time, the increased adhesiveness of the drug to mucosal surfaces (Ponchel et al 1997) offers a prolonged residence time for the drug at the absorption site. This ability of Nano suspensions to offer quick onset of action initially and then controlled release of the active moiety is highly beneficial and is required by most pulmonary diseases. Moreover, as Nano suspensions generally contain a very low fraction of micro particulated drug, they prevent unwanted deposition of particles in the mouth and pharynx, leading to decreased local and systemic side-effects of the drug. Additionally, because of the Nano particulate nature and uniform size distribution of Nano suspensions, it is very likely that in each aerosol droplet at least one drug nanoparticle is contained, leading to even distribution of the drug in the lungs as compared to the micro particulate form of the drug. In conventional suspension aerosols many droplets are drug free and others are highly loaded with the drug, leading to uneven delivery and distribution of the drug in the lungs. Nano suspensions could be used in all available types of nebulizer. However, the extent of influence exerted by the nebulizer type as well as the nebulization process on the particle size of Nano suspensions should be ascertained. Budesonide, a poorly water-soluble corticosteroid, has been successfully formulated as a Nano suspension for pulmonary delivery (Mü’ Iler & Jacobs 2002b). A good relationship was obtained between increasing the drug concentration in the formulation and the number of micrograms of drug delivered per 2s actuation.
Targeted drug delivery:

The need to target drugs to specific sites is increasing day by day as a result of therapeutic and economic factors.Nano particulate systems have shown tremendous potential in targeted drug delivery, especially to the brain (Schroeder et al. 1998; Kreuter 2001). Successful targeting of the peptide dalargin to the brain by employing surface-modified polyisobutyl cyanoacrylate nanoparticles has been a major achievement in targeted delivery (Kreuter et al. 1997). Likewise, Nano suspensions can be used for targeted delivery as their surface properties and in-vivo behavior can easily be altered by changing either the stabilizer or the milieu. Their versatility and ease of scale-up and commercial production enables the development of commercially viable Nano suspensions for targeted delivery. Natural targeting of MPS by Nano suspensions has already been described. However, the natural targeting process could pose an obstacle when macrophages are not the desired targets. Hence, in order to bypass the phagocytic uptake of the drug, its surface properties need to be altered, as in the case of stealth liposomes (Gregoriades 1995; Allen 1997; Lasic et al. 1997; Papisov 1998; Woodle 1998; Vyas et al. 2000). The engineering of stealth Nano suspensions (analogous to stealth liposomes) by using various surface coatings for active or passive targeting of the desired site is the future of targeted drug delivery systems. Another good example is targeting of Cryptosporidium parvum, the organism responsible for cryptosporidiosis, by using surface-modified mucoadhesive Nano suspensions of bupravaquone (Kayser 2001; Müller & Jacobs 2002a). A considerable difference has been observed in the efficacy of bupravaquone Nano suspensions when delivered with and without mucoadhesive polymers (Kayser 2001; Müller & Jacobs 2002a). Mucoadhesive bupravaquone Nano suspensions, because of their prolonged residence at the infection site, revealed a 10-fold reduction in the infectivity score of Cryptosporidium parvum as compared to the Bupravaquone Nano suspensions without mucoadhesive polymers. Similarly, conditions such as pulmonary aspergillosis can easily be targeted by using suitable drug candidates, such as amphotericin B, in the form of pulmonary Nano suspensions instead of using stealth liposomes (Kohno et al. 1997). With the advent of polymeric Nano suspensions loaded with drug (as described in the section on ocular delivery), it should be possible to target sites, such as the colon, or bacteria, such as H. pylori, by suitable modifications in the formulation strategy. Overall, Nano suspensions have indicated a good potential in targeted drug delivery but this has yet to be fulfilled.

Figure 3: Polymeric Micelles.

Polymeric Micelles:

Despite the great amount of scientific data amassed on tuberculosis (TB), an infection that has afflicted the human race for thousands of years, there is still no victory in sight over the disease, which today represents a severe problem for public health in many parts of the world, especially in the poorer countries. With the constantly growing number of multidrug resistant strains and the spread of AIDS, this destroys patients’ immunity, leaving them much more susceptible to mycobacterial infection; the rates of incidence and prevalence of TB have been rising and could threaten the socioeconomic development of affected countries, in view of the fact that both TB and AIDS affect, in the main, people in their most productive years, aged 15-49.

While it is true that very useful tuberculostatic products exist, both for treatment and prophylaxis, the known toxic side-effects of these drugs, the infection of patients by the M. avium complex and their lack of adherence to the course of treatment, are all factors that make the ongoing search for improved drugs absolutely indispensable. As a rule, new drugs are introduced by modifying molecules with known characteristics, often with the help of computer-aided design techniques. Synthetic routes that are designed to begin with a known drug and make planned improvements in some of its properties, particularly in its pharmacokinetics (as is the case in delayed action prodrugs) are often used. Prodrugs are chemicals with little or no pharmacological activity, undergoing biotransformation to a therapeutically active metabolite. In the prodrug approach, the physicochemical properties of the parent drug are transiently modified with a promoiety or carrier 4. The objectives of a prodrug strategy are: to solve problems resulting from poor solubility, insufficient chemical stability or poor organoleptic properties; reduced systemic toxicity; improved oral bioavailability, by improving the oral absorption of the drug and/or by decreasing its presystemic metabolism. Other objectives are to improve absorption, lengthen the duration of action of the drug by slow metabolic release, and finally achieve the organ/tissue-selective delivery of an active agent. Even though great advances have been made in polymeric drugs, the practice of conjugating hydrophobic drug moieties in dense clusters along the polymer chain of a carrier molecule and, not infrequently, the low water solubility of the carrier itself, can easily result in the precipitation of the polymer derivative, and often does. To overcome this problem, a promising technique is to make polymer drugs that take the form of micelles. In line with this approach, micelle-forming polymer derivatives of the initial-phase anti-tuberculostatic drugs pyrazinamide, isoniazid and rifampin were synthesized in this study.

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These derivatives were characterized by determining the critical micelle concentration (CMC) and the mean diameter of the micelles, and then tested for activity against several mycobacterial strains, such as virulent M. tuberculosis and M. avium.

APPLICATIONS:

SOLUBILIZATION:

The micellar core is a compatible micro environment and a hub for incorporating water-insoluble guest molecules. The hydrophobic molecules can be covalently coupled to the block copolymers or physically incorporated into the hydrophobic core of micelles. The solubilization process leads to enhancement of their water solubility and there by bioavailability. It is often observed that the gastrointestinal (GI) uptake of particles is affected significantly by particle size. A 15 to 250-fold higher uptake efficiency of particles approximately 100 nm in diameter by the GI tract was noted than that of the micrometer-sized particles. Thus, polymeric micelles (Nano sized) elevate uptake and enhance bioavailability. The extent of solubilization depends upon the micellization process, the compatibility between the drug and the core forming block, chain length of the hydrophobic block, concentration of polymer, and temperature. Above CMC, there is a sharp increase in the solubility of drug as it gets more space to occupy in the aggregates of the hydrophobic part of the micelle. The occupancy of the core region by drug leads to an increased RC of the micelle. It is worth mentioning that the core region has limited capacity for accommodation, for instance, Pluronic P85 has a core region which is 13% of the whole micelle weight. The influence on solubilization capacity of hydrophobic block length has been examined for griseofulvin in polyoxyethylene and polyoxybutylene copolymer micelles with varying number of hydrophobic block lengths and hydrophilic block lengths sufficient for formation of spherical micelles. It was found that the solubilization capacity was dependent on the hydrophobic block length up to a certain extent (15 units of hydrophobic block), after which the solubilization capacity became independent of the same. Dong and coworkers also studied the effect of hydrophobic block length on solubilization of toluene in diblock and triblock polyurethane surfactants. It was concluded that solubilization capacity of polyurethane surfactants increased with an increase in the hydrophobic segment for the same block chain structure.

TARGETING:

Targeting via polymeric micelles is usually achieved by one of the following approaches; the enhanced permeability and retention effect, stimuli sensitivity, complexing specific targeting ligand molecules to the micelle surface, or by coupling monoclonal antibodies to the micelle corona, i.e. active targeting using immunomicelles.

Enhanced Permeability and Retention Effect (EPReffect):

Owing to their nanoscopic size, polymeric micelles passively accumulate at the interstitial spaces of various pathological sites by extravasating leaky capillaries (especially of solid tumors). They also have been shown to distribute to some of the cytoplasmic organelles, and infarct tissues, infected areas, inflammatory sites that have compromised barrier function. As the polymeric micellar drug carriers cannot pass through walls of normal blood vessels, decreased side effects of the drug are observed. In tumor neovascularure, there is a poorly developed lymphatic drainage system that leads to enhanced retention of polymeric micelles within the solid tumor as micelles are not efficiently cleared. This feature allows prolonged circulation of polymeric micelles in the circulatory system upon administration. Due to these characteristics, it is possible to achieve passive drug targeting using polymeric micelles. The hyper permeability of tumors associated with the EPReffect is based on excessive production and secretion of vascular permeability factors stimulating extravasation within cancerous tissue. Commonly secreted chemicals are vascular endothelial growth factor bradykinins, nitric oxide, prostaglandins, enzyme collagenase, and peroxynitrile. Vetvicka and his associates formulated a micellar drug delivery system designed to prolong the blood circulation time and maximize the efficiency of the EPR effect. They prepared doxorubicin conjugated poly (ethylene oxide) block-poly(allylglycidyl ether) micellar system that circulated for long time and released doxorubicin efficiently at the tumor site because of the acidic pH prevailing at the tumor site. This also leads to destabilization and disruption of the micellar system generating free diblock unimers that could be excreted. Maitani et al. developed polymeric micelles composed of various poly(ethylene glycol)-poly(aspartate ester) block copolymers incorporating camptothecin, a naturally occurring cytotoxic alkaloid. The micellar system solubilized the poorly water soluble drug and a stable formulation of camptothecin-loaded micelles was obtained. The stability of the formulation was found to strongly depend on the amount of benzyl esters and length of the PEG. The drug-loaded micelles were potentially delivered to tumor sites owing to the EPR effect.

Stimuli-Sensitivity:

For ideal drug targeting, there should not be any drug release from the micelle during circulation. The drug should be released only after the polymeric micelles accumulate at the targeted tissue, by means of some internal trigger such as pH, particular enzyme, etc. or by an external trigger including temperature, light, ultrasound or magnetic field. Depending on the stimulus applied varied responses may be observed including disruption of the structure, changes in shape, volume, permeation rates, hydration state, swelling/collapsing, hydrophilic/hydrophobic surface, or conformational changes. Destabilization of micelles as a result of stimulation by either physiological or external trigger is termed as 'stimuli-sensitivity' or 'environmental sensitivity' of the micelles. Release of drug from the micellar system is dependent on the exploitation of differences that exist in normal tissues and pathological tissues. Such a release mechanism from polymeric micelles is also termed as 'intelligent delivery' or 'smart delivery' by other researchers.
Acid-Sensitive Polymeric Micelles:

There are a number of pH gradients that exist in normal and pathophysiological states inside the body. Acid-sensitive or pH-sensitive polymeric micelles exploit these differences in pH for drug targeting. In tumors and inflammatory tissues a mildly acidic pH is encountered (pH approx. 6.8). This is a slightly low value as compared with the pH of blood and normal tissues (pH approx. 7.4). Micelles can also be taken up into the cell by the process of endocytosis and may as well enter cell organelles as endosomes, lysosomes, etc. The pH value inside these organelles is nearly 5.5. This has served as the basis for the development of pH-sensitive polymeric micelles. e.g., negatively charged oligo/poly (nucleic acids) can be delivered intracellular by complexing them with cationic polymers. Once into endosomes, these are deprotonated causing disruption of endosomal membrane and releasing nucleic acids in the cytosol. Two main approaches that have been used for developing pH sensitive systems are: involvement of a titrable group into the copolymer, and inclusion of labile linkages that are destabilized in acidic conditions. Incorporation of titrable groups such as amines, carboxylic acids into the backbone of the copolymer leads to an alteration of the solubility of the polymer upon protonation. This in effect may disrupt the micellar structure. Inclusion of acid-labile linkages, such as benzoic imine linkage, in polymeric structures has shown to cause change in micellar integrity or complete destruction of the micellar structure when these polymers encounter low-pH environment.

Thermo sensitive Polymeric Micelles:

The thermo sensitive micelles undergo a structural change as a response to temperature increase, resulting in the deposition of the drug and easier drug absorption by cells. Thermo sensitive polymers at a certain temperature produce a volume phase transition associated with a sudden change in the solvation state. This transition temperature is termed as critical solution temperature. Polymers solubilized upon heating possess an upper critical solution temperature, and those which become insoluble possess lower critical solution temperature (LCST). With regard to the thermal targeting strategy, LCST is the most important parameter. Temperature changes can be internal, e.g., hyperthermia during inflammation, or can be external. Heat can be generated inside target tissues by locally applied ultrasound or locally applied high frequency causing the oscillation of target-accumulated magneto-sensitive micelles. Liu et al. demonstrated the use of poly(N-isopropylacrylamide-co-acrylamide)-b-poly(D,L-lactide) copolymer in tumor targeting of docetaxel. They observed that hyperthermia greatly enhanced the targeting efficacy of drug-loaded micelles and also helped in reduction of toxicity of drug.

Complexing Targeting Ligand Molecules to Micelles:

An impressive strategy to enhance cellular internalization of polymeric micelles at desired target tissue is attachment of cell-specific ligands on the surface of these Nano carriers. Thus, covalent attachment of cell specific ligands, e.g., sugars, peptides, and monoclonal antibodies, on the surface of polymeric micelles has been pursued to enhance drug delivery to various cells. For tumor targeting, cancer-specific peptides are more appropriate as peptides can easily be derivatized and engineered to achieve better in vivo stability and tissue specificity. In this context, Lavasanifar et al. conjugated an arginine-glycine-aspartic acid (RGD) containing peptide as a ligand that can recognize adhesion molecules overexpressed on the surface of metastatic cancer cells, to the surface of poly(ethylene oxide)-block-poly(caprolactone) micelles. It was found that micelles were good ligand-targeted carriers for enhanced drug delivery to metastatic tumor cells. Torchilin et al. used the overexpression of Peripheral Benzodiazepine Receptor (PBR) in certain cancers for targeting such tissues. Selective ligands to the PBR may induce apoptosis and cell cycle arrest. Thus, polyethylene glycol-phosphatidylethanolamine PBR-targeted micellar drug delivery system loaded with paclitaxel was prepared. They demonstrated the use of this system to reveal significantly enhanced toxicity against some cancerous cells.

Active Targeting using Immunomicelles:

Attachment of antibodies to micelle surface provides the broadest opportunities in terms of diversity of targets. Thus, many researchers have tried to exploit this opportunity by covalently attaching an antibody to polymeric micelles for generating the ‘immunomicelles’. To demonstrate the effectiveness of using immunomicelles in targeting of cancer, Torchilin et al. solubilized paclitaxel and camptothecin in mixed micelles of polyethylene glycol-phosphatidyl ethanolamine and vitamin E. These micelles were additionally modified with antinucleosome monoclonal antibody 2C5 (mAb 2C5), which can specifically bring micelles to tumor cells in vitro. These mixed micelles and mAb 2C5-immunomicelles demonstrated significantly higher in vitro cytotoxicity against various cancer cell lines.

Figure 4: LIPOSOMES.
LIPOSOMES

Liposomes were first produced in England in the 60’s, by Bangham who was studying phospholipids and blood clotting. According to legend, he was experimenting with new laboratory equipment, and he made a noted observation about phospholipids forming closed multilamellar vesicle spontaneously in aqueous solution which took two years to be proved. The phospholipid reorganisation in aqueous solution is mainly driven by the hydrophobic effect which organizes amphiphilic molecules (phospholipids) so as to minimize entropically unfavorable interactions between hydrophobic acyl-chains and surrounding aqueous medium. This effect is further settled by various intermolecular forces such as electrostatic interactions, hydrogen bonding, as well as Vanderwaals and dispersion forces. Liposomes were defined as an artificial microscopic vesicle consisting of a central aqueous compartment surrounded by one or more concentric phospholipid layers (lamellas). Furthermore, hydrophilic (in the aqueous cavity), hydrophobic (within lipidic membrane) and amphiphilic substances are able to be incorporated within these vesicles developing large potential applications. Numerous researchers have worked with these structures since Bangham’s discovery, making of liposomes the most popular Nano carrier systems. Liposomes can be classified in terms of composition and mechanism of intracellular delivery into five types
(i) Conventional liposomes;
(ii) pH-sensitive liposomes;
(iii) Cationic liposomes;
(iv) Immuneliposomes and
(v) Long-circulating liposomes

Applications
New drug delivery systems such as liposomes are developed when an existing formulation is not satisfactory and reformulation offers superior therapeutic efficacy and safety over the existing formulation. Indeed, liposome formulations of some drugs have shown a significant increase in therapeutic efficacy and/or therapeutic indices in preclinical models and in humans, compared to their non-liposomal formulations. The therapeutic applications of liposomes generally fall into several categories briefly described below.

Formulation aid

Hydrophobic drugs such as cyclosporin and paclitaxel are usually formulated in surfactants and organic co-solvents for systemic administration in humans. These solubilizers may cause toxicity at the doses needed to deliver the drug. In contrast, liposomes are made up of lipids which are relatively non-toxic, non-immunogenic, biocompatible and biodegradable molecules, and can encapsulate a broad range of water-insoluble (lipophilic) drugs. Currently, liposomes or phospholipid mixtures are being used as excipients for preparing better-tolerated preclinical and clinical formulations of several lipophilic, poorly water-soluble drugs such as amphotericin B. In preclinical studies, liposomes have been evaluated as a vehicle for the delivery of paclitaxel and its analogs as an alternative to the cremophor/ethanol vehicle. Paclitaxel liposomes were able to deliver the drug systemically and increase the therapeutic index of paclitaxel in human ovarian tumor models.

Intracellular drug delivery
Drugs with intracellular targets/receptors are required to cross the plasma membrane for pharmacological activity. Liposomes can be used to increase cytosolic delivery of certain drugs such as N-(phosphonacetyl)-L-aspartate (PALA) which is normally poorly taken up into cells. PALA is taken up into the tumor cells through fluid-phase endocytosis (pinocytosis) and it diffuses out into the cytoplasm as the endosome pH drops. However, pinocytosis is very limited in its efficiency. Liposomal delivery of drugs which normally enter the cells by pinocytosis can be very effective because liposomes can contain greater concentrations of drug compared to the extracellular fluid and the endocytosis process by which negatively charged liposomes are predominantly taken up by the cells, is more efficient than pinocytosis. For example, the potency of PALA encapsulated liposomes was up to 500-fold greater against human ovarian tumor cell lines than that of free PALA.

Sustained release drug delivery
Sustained release systems are required for drugs such as cytosine arabinoside (Ara-C) that are rapidly cleared in vivo and require plasma concentrations at therapeutic levels for a prolonged period for optimum pharmacological effects. It is now possible to design sustained release liposome formulations with an extended circulation half-life and an optimized drug release rate in vivo. For example, Ara-C encapsulated in LCL is effective as a prolonged release system in the treatment of murine L1210/C2 leukemia. Conventional liposomes which localize by phagocytosis in the cells of RES may also act as a sustained release depot by slowly leaking drugs from RES into the general circulation.
Gene therapy

A number of systemic diseases are caused by lack of enzymes/factors which are due to missing or defective genes. In recent years, several attempts have been made to restore gene expression by delivery of the relevant exogenous DNA or genes to cells. Cationic liposomes have been considered as potential non-viral human gene delivery system. They are usually composed of a cationic lipid derivative and a neutral phospholipid (DOPE). The latter is required by certain cationic lipids to form stable liposomes. Some of the widely used cationic liposome formulations are: lipofectin (DOTMA: DOPE, 1:1); lipofectamine (DOSPA: DOPE, 3:1); transfecta (DDAB: DOPE, 1:3); cytofectin (DMRIE: DOPE); transfectam (DOGS) and DC-cholesterol. The negatively charged genetic material (e.g., plasmid) is not encapsulated in liposomes but complexed with cationic lipids by electrostatic interactions. Plasmid-liposome complexes are thought to enter the cell by fusion with the plasma or endosome membrane.

Allovec--7, a gene transfer product is currently in clinical trials (phase I/II) as an immunotherapeutic agent for the treatment of metastatic melanoma, renal cell and colorectal carcinoma. Allovec-7 is composed of a plasmid containing the gene for the major histocompatibility complex antigen HLA-B7 with fl-2 microglobulin formulated with the cytofectin (DMRIE: DOPE). The ongoing clinical trials have indicated that intralesional injection of Allovec-7 can be performed safely and have demonstrated antitumor activity in some patients. Plasmid-liposome complexes have many advantages as gene transfer vehicles over viral-based vectors: (i) these complexes are relatively nonimmunogenic because they lack proteins; (ii) liposomes or lipid complexes can be used for transfection of large-sized genetic material; and (iii) viruses, unlike plasmid-liposome complexes, may replicate and cause infections. However, there are several problems limiting the application of liposomes as a gene delivery system.

Site-avoidance delivery:

Drugs used in the treatment of diseases like cancer usually have a narrow therapeutic index(TI) and can be highly toxic to normal tissues. The toxicity of these drugs may be minimized by decreasing delivery to critical normal organs. It has been shown that even a small reduction in distribution of the drug to critical organs by encapsulation in liposomes can significantly reduce the drug toxicity (Szoka, 1991). Liposomes are taken up poorly by tissues such as heart, kidney, and GI tract, which are major sites for toxic side-effects of a variety of antineoplastic drugs. Thus, liposome formulation may improve the TI by altering the bio distribution of drug away from drug sensitive normal tissues. For instance, free amphotericin B and doxorubicin produce severe dose-limiting nephrotoxicity and cardiac toxicity, respectively. Reformulation of these drugs in liposomes results in reduced toxicity with no change in therapeutic efficacy. Liposome formulations of amphotericin B and doxorubicin have now been approved for clinical use.

Site-specific targeting:

Site-specific delivery, the concept first proposed by Paul Ehrlich (Ehrlich, 1906) involves the delivery of a larger fraction of drug to the target site and therefore, reducing exposure to normal tissues. Liposomes have been employed for accomplishing both passive and active targeting of drugs.

Intraperitoneal administration:

Direct administration of antineoplastic agents into the intraperitoneal (i.p.) cavity has been proposed to be therapeutically advantageous for cancers that develop in or metastasize to the peritoneal cavity. Intraperitoneal chemotherapy has been somewhat unsuccessful for free drugs because of relatively fast clearance of the drugs from the i.p. cavity resulting in lowered concentrations at the site of action. However, the clearance of liposomes from the peritoneal cavity is significantly slower than that of free drug and therefore, higher drug concentrations can be achieved in the proximity of the target site for extended periods of time with the use of liposome formulations. Furthermore, reformulation of erosive drugs in liposomes has been shown to reduce local drug toxicity such as dermal toxicity of doxorubicin. An increase in TI of paclitaxel in liposomes after i.p. administration may also be due to a reduction in local (abdominal) toxicity of the drug.

Immunological adjuvants in vaccines:

Liposomes can encapsulate antigens in their aqueous space or incorporate in the bilayer depending on the lipophilicity of the antigen. Liposomes were first used as immunological adjuvants in order to enhance the immune response to encapsulated diphertheria toxoid. Since then, liposomes have been used as nontoxic adjuvants with bacterial, viral, protozoan, tumor and other antigens. The tendency of liposomes to interact with macrophages in RES is exploited in this approach (passive targeting). The mechanism by which liposomes cause increases in antigens immune response is not fully understood. However, augmentation of liposomal adjuvant city can be achieved by co-administration of liposome encapsulated antigen with other adjuvants such as lipid A, lipopolysaccharides, muramyldipeptide and interleukin (IL-2).

Furthermore, antibody-mediated targeting of liposomal to antigen-presenting cells may also improve immunostimulatory effects. The influence of physicochemical properties of the liposomes such as charge density, membrane fluidity and epitope density, on the immune response of the antigen has been extensively studied. For instance, liposome formulations of inactivated encephalomyocarditis and Semliki Forest viruses were significantly more immunogenic when charged phospholipids were used compared to neutral lipids. The phase transition temperature (To) of the lipids also appears to influence immunogenicity. For example, immunogenicity of hapten was higher in liposomes composed of lipids with a high Tc than in those with a low Tc. Recently, the first liposome-based vaccine (liposomes containing inactivated hepatitis A virions) was approved for human use in Switzerland and currently, several other liposome-based vaccines are in clinical trials.
Dendrimers:

The discovery and creation of new drugs is a timely and costly process. It is estimated that every new drug takes 12 to 15 years to develop, at a cost of over $800 million. A more efficient approach would be the devising of effective drug delivery systems for already developed experimental drugs that failed to make it to the market. Controlled release systems can improve the effectiveness of drug delivery by sustained release of the compound over time or by release at a specific target. By controlling the time and location of delivery, side effects can be minimized and drug efficacy can be maximized, thus leading to a lower dosage for patients. Methods to achieve controlled release include chemical or enzymatic reaction, diffusion through a matrix, or solvent activation. Currently, the two common drug delivery systems are liposomes and polymeric systems. These both have limited applications, as liposome-based systems have poor stability and difficulty targeting specific tissues, and linear polymers are polydisperse. Dendrimers offer advantages including a lower polydispersity index, multiple sites of attachment, and a controllable, well-defined size and structure that can be easily modified to change the chemical properties of the system. In addition, macromolecules such as dendrimers have an enhanced permeability and retention effect that allows them to target tumor cells more effectively than small molecules. Dendrimers have applications in gene and antisense therapy, magnetic resonance imaging, and in boron neutron capture therapy. Advances in dendrimer delivery systems, biodegradable dendrimers, and release from dendrimers can be applied to drug delivery in addition to other applications.

Application:

Therapeutic Application:
- Dendrimer in photodynamic therapy
- Dendrimers for Boron Neutron capture therapy

Diagnostic Application:
- Dendrimers as MRI contrast agent
- Dendrimers as X-Ray contrast agent
- Dendrimer as molecular probe

Pharmaceutical Application:
- Dendrimers in pulmonary drug delivery
- Dendrimers in Transdermal drug delivery
- Dendrimers in ocular drug delivery
- Dendrimers in oral drug delivery
- Dendrimers for controlled release drug delivery
- Dendrimers in targeted drug delivery
- Dendrimers in gene delivery
- Dendrimers as solubility enhancer
- Cellular delivery using dendrimers carrier
- Dendrimers based product in cosmetics
- Dendrimers based commercial products
Dendrimers in Gene Delivery:
Dendrimers can be used as a carrier in gene therapy. Example- PAMAM dendrimers have terminal amino groups which interact with phosphate group of nucleic acid. So PAMAM dendrimers have been tested as a genetic material vector. Super Fect TM is a transfection reagent, it consist of activated dendrimers. Activated dendrimers can carry a large amount of genetic material than viruses. Super Fect- DNA complex are highly stable and have high transfection efficiency. The high transfection efficiency is due to their well-defined shape and low pk of the amines.

Dendrimers as Solubility Enhancer:
Dendrimers are unimolecular micellar in nature because these have both hydrophobic and hydrophilic layer. Hydrophilic layer forms the core and hydrophilic layer forms the outer surface. Dendrimers do not have a critical micelle concentration. Due to these properties dendrimers enhance the solubility of poorly soluble drug by forming covalent, non-covalent complexes with drug molecules and hydrophobes.

Dendrimers as Cellular Drug Delivery Carrier:
Pure drug (Ibuprofen) entered into the cell in 3 hours but the dendrimers ibuprofen complexes entered into the cell in 1 hour. So these result shows that dendrimers can carry the complex drug efficiently inside the cell.

Dendrimers in Targeted and Controlled Release Drug Delivery:
The dendrimers facilitate the passive targeting of drug to solid tumors. This is due to their enhanced solubility and plasma circulation time. EPR (Enhanced Permeation and Retention) in tumors tissues leads to reduce cytotoxicity of anticancer drug and increased uptake by cancer cell lines. Example- Doxorubicin.

Dendrimers in Cosmetics:
Dendrimers have a great contribution on cosmetics. Various cosmetics industry used dendrimers in the formulation. L’Oreal has a patent for using dendrimers in the production of cosmetics like mascara or nail polish. Unilever also have a patent for dendrimers in the production of formulation for used in spray, gels and lotions.

Applications of Dendrimers in Waste Water Treatment:
Dendritic polymers are used in the purification of water contaminated by toxic metal ion, inorganic solute and organic solutes.

Magnetic nanoparticles:
Magnetic nanoparticles offer some attractive possibilities in biomedicine. First, they have controllable sizes ranging from a few nanometers up to tens of nanometers, which places them at dimensions that are smaller than or comparable to those of a cell (10–100μm), a virus (20–450 nm), a protein (5–50 nm) or a gene (2 nm wide and 10–100 nm long). This means that they can ‘get close’ to a biological entity of interest. Indeed, they can be coated with biological molecules to make them interact with or bind to a biological entity, thereby providing a controllable means of ‘tagging’ or addressing it. Second, the nanoparticles are magnetic, which means that they obey Coulomb’s law, and can be manipulated by an external magnetic field gradient. This ‘action at a distance’, combined with the intrinsic penetrability of magnetic fields into human tissue, opens up many applications involving the transport and/or immobilization of magnetic nanoparticles, or of magnetically tagged biological entities. In this way they can be made to deliver a package, such as an anticancer drug, or a cohort of radionuclide atoms, to a targeted region of the body, such as a tumor. Third, the magnetic nanoparticles can be made to resonantly respond to a time-varying magnetic field, with advantageous results related to the transfer of energy from the exciting field to the nanoparticle. For example, the particle can be made to heat up, which leads to their use as hyperthermia agents, delivering toxic amounts of thermal energy to targeted bodies such as tumor’s, or as chemotherapy and radiotherapy enhancement agents, where a moderate degree of tissue warming results in more effective malignant cell destruction. These, and many other potential applications, are made available in biomedicine as a result of the special physical properties of magnetic nanoparticles16.
Nano shells coated with Gold:

Gold Nano shells are spherical particles with diameters typically ranging in size from 10 to 200nm. They are composed of a dielectric core covered by a thin gold shell. As novel nanostructures, they possess a remarkable set of optical, chemical, and physical properties, which make them ideal candidates for enhancing cancer detection, cancer treatment, cellular imaging and medicinal bio-sensing. Gold Nano shells are unique in that they combine many ideal features in a single particle. As a direct result of Nano scale resonance phenomena, gold Nano shells have very large optical absorption and scattering cross-sections, which render them highly suitable as contrast agents for imaging. They can be tuned to preferentially absorb or scatter light at specific wavelengths in the visible and near-infrared (NIR) regions of the spectrum. In the NIR ‘tissue window’, light penetration into tissue is optimal. Nano shells tuned to absorb NIR radiation are particularly useful as mediators of photo thermal cancer therapy because they efficiently convert absorbed radiation into heat, and are thermally stable at therapeutic temperatures. Furthermore, Nano shells preferentially accumulate at tumor sites due to their Nano scale dimensions. The inert gold surface of Nano shells provides several advantages, including biocompatibility, no cytotoxicity, and it also facilitates conjugation to monoclonal antibodies or other biomolecules for both active tumor targeting and bio-sensing applications. The first Stage I clinical trials using Nano shells as therapeutic agents to treat head and neck cancers are set to commence in 2008. Over the past few years, the pace of research in this field has accelerated rapidly, as have the number of potential biomedical applications for Nano shells.17

Quantum dots:

A quantum dot is a semiconductor nanostructure that confines the motion of conduction band electrons, valence band holes, or excitons (bound pairs of conduction band electrons and valence band holes) in all three spatial directions. The confinement can be due to electrostatic potentials (generated by external electrodes, doping strain, impurities), the presence of an interface between different semiconductor materials (e.g., core-shell Nano crystal systems), the presence of the semiconductor surface (e.g., semiconductor Nano crystal), or a combination of these. Quantumdots are particularly significant for optical applications due to their theoretically high quantum yield. The ability to tune the size of quantum dots is advantageous for many applications and it is one of the most promising candidates for use in solid-state quantum computation and diagnosis, drug delivery, tissue engineering, catalysis, filtration and also textiles technologies.18

Quantum dots (QDs) are semiconducting materials consisting of a semiconductor core (CdSe), coated by a shell (e.g., ZnS) to improve optical properties, and a cap enabling improved solubility in aqueous buffers. They are neither atomic nor bulk semiconductors. Their properties originate from their physical size, which ranges from 10–100 Å in radius. Due to their bright fluorescence, narrow emission, broad UV excitation and high photo stability QDs have been adopted for in vitro bio imaging for real time monitoring or tracking of intracellular processes for longer time. Quantum-dots have a large impact on some important development in different medical areas like diagnostic tools (magnetic resonance imaging, MRI), in vitro and in vivo detection and analysis of biomolecules, immunological, DNA hybridization, development of non-viral vectors for gene therapy, transport vehicles for DNA, protein, drugs or cells, time graded fluorescence imaging of tissue, labeling of cells and as therapeutic tools for cancer treatment.19

Quantum dots (QD) are small (2–10 nm) colloidal fluorescent semiconductor Nano crystals composed from 10–50 atoms of groups II–IV or III–V of the periodic table. Their structure consists of a metalloid crystalline core and a shell that protects the core and renders the QD available for in vivo applications. The size and shape of quantum dots can be controlled precisely, properties that determine their absorption and light emission. One of the most valuable properties of QD is their fluorescence spectrum, which makes them optimal fluorophores for biomedical imaging. Fluorescent QD can be conjugated with bioactive moieties or specific ligands (e.g., receptor ligands and antibodies). QD are stable for months without degradation or alteration. QD are mostly used as long-term, high-sensitivity and multicontrast imaging agents for detection and diagnosis of cancer in vivo. Other examples of QD applications include transistors, solar cells, and quantum computing. Nevertheless, because they are composed of hazardous heavy metals, it is important to be cautious about their toxicity.20

Ferro fluids:

Ferro fluids (known also as magnetic fluids) are a special category of smart nanomaterials. In particular, magneto- controllable Nano fluids. These types of Nano fluids are colloids of magnetic nanoparticles, such as Fe3O4, γFe2O3, CoFe2O4, Co, Fe or Fe-C, stably dispersed in a carrier liquid. Consequently, these nanomaterial’s manifest simultaneously fluid and magnetic properties. Macroscopically, the introduction of magnetic forces into the fundamental hydrodynamic equations for the quasihomogeneous magnetizable liquid medium gives rise to the magneto hydrodynamics of magnetic Nano fluids (Ferro fluids), known also as Ferro hydrodynamics and opens up an entire field of new phenomena and promising applications. From a microscopic point of view, long-range, attractive van der Waals and magnetic forces are ubiquitous and therefore must be balanced by Columbic, steric or other interactions to control the colloidal stability of dispersed nanoparticle system, even in intense and strongly non-uniform magnetic field, specific to most of the applications. Many of the envisaged applications, e.g., rotating seals or bearings, require magnetic fluids with high magnetization and at the same time, with long-term colloidal stability. These requirements are difficult to fulfill simultaneously and imply severe conditions on the stabilization procedures applied during the synthesis of magnetic Nano fluids. The composition, structure and properties of various types of Ferro fluids will be presented, referring also to technological and biomedical applications envisaged for these Nano fluids.21
CONCLUSION

Nanotechnology has been attracting significant attention from the media as well as government funding in recent years. Surveyed company representatives point to the strategic relevance of nanotechnology as an innovation driver and success factor in their enterprises. Today, there are estimates 305 Nano life science company’s across the globe. The United states accounts for the majority of these company’s (52%), followed by Germany (21%).

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