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Nanoparticles as Carrier System in Pharmaceutical

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ABSTRACT

Nanoparticles are of particular interest due to a growing awareness of their potential effects on human health and the protection of the environment and due to the increasing production of man-made nanoparticles. The development of drug formulations based on nanoparticles has given opportunities to tackle and treat difficult diseases. The scale of nanoparticles varies from 100 to 500 nm. Constructions and assemblies of nanoparticles are nanoscale and include entities such as drugs, enzymes, DNA / RNA, viruses, cellular lipid bilayers, cellular receptor sites, and immunologically important antibody variable regions, and are involved in events of nanoscale proportions. The advent of these nanotherapeutics/diagnostics would provide a deeper understanding of human longevity and illnesses like cancer, cardiovascular disease, and genetic disorders. The nanoparticles can be formed into smart devices, encasing therapeutic and imaging agents as well as carrying stealth properties by controlling the size, surface characteristics and the material used. Also, these devices can provide drug delivery to different tissues and controlled-release therapy. Such controlled and continuous drug delivery decreases the risk associated with the drug and improves patient compliance with less regular doses. Nanotechnology is effective in the treatment of cancer, AIDS and many other diseases and has also made advances in diagnostic testing.

INTRODUCTION

Nanotechnology is the study of very small structures. Pharmaceutical Nanotechnology involves the formation and development of small structures like atoms, molecules or compounds of size 0.1 to 100 nm into structures that can be further developed into special devices with desired characteristics and properties to give therapeutic effect [1]. Particles having a diameter in the range between 10-100 nm are known as Nanoparticles. Nanoparticles are used in many different applications and created by many different processes. Their measurement and characterization pose interesting analytical challenges. They are used as a targeted delivery system for the delivery of small and large molecules by changing their pharmacodynamics and pharmacokinetic properties [2]. They can be defined as a system that contains active ingredient dissolved, encapsulated or adsorbed in a matrix material which is used as target delivery system [3].

Nanomedicine is one of the most intensive areas of research in nanotechnology and is applied widely for the prevention, diagnosis, and treatment of diseases. It is utilized in pharmaceutical sciences with the objectives of reducing toxicity and minimizing side effects of drugs by targeting them to the specific site of action, reducing their dose through improved bioavailability; reducing dosing frequency by controlling drug release into the human body; and improving shelf life by enhancing their stability. This ultimately contributes to increased safety, efficacy, patient compliance and extended shelf life of drugs and finally reduced healthcare costs [4, 5, 6]. For better development of the nanoparticulate systems, it is essential to understand the pharmaceutically relevant properties of Nanoparticles. There is significant interest in recent years in developing Nanoparticles as a drug/gene delivery system. Nanoparticles are colloidal particles that range in size from 10 to 1000 nm in diameter and are formulated using biodegradable polymers 5-10 in which a therapeutic agent can be entrapped, adsorbed, or chemically coupled.

IMPORTANT OF NANOPARTICLE IN FORMULATION DEVELOPMENT

A nanoparticle is notable that the efficiency of most drug delivery systems is directly related to particle size (excluding intravenous and solution). Due to their small size and large surface area, drug Nanoparticles show increase solubility and thus enhanced bioavailability, additional ability to cross the blood-brain barrier (BBB), enter the pulmonary system and be absorbed through the tight junctions of endothelial cells of the skin [7]. Specifically,

Nanoparticles made from natural and synthetic polymers (biodegradable and non-biodegradable) have received more attention because they can be customized for targeted delivery of drugs, improve bioavailability, and provide a controlled release of medication from a single dose; through adaptation, the system can prevent endogenous enzymes from degrading the drug [8]. The benefit of pharmaceutical companies taking advantage of this new technology is that nanotechnology gives new life to those drugs that were previously considered unmarketable due to low solubility and bioavailability, and high toxicity and marked side effects [9].

Nanotechnology is also opening up new opportunities in implantable delivery systems, which are often preferable to the use of injectable drugs because the latter frequently display first-order kinetics (the blood concentration goes up rapidly, but drops exponentially over time). This rapid rise may cause difficulties with toxicity, and drug efficacy can diminish as the drug concentration falls below the targeted range. In contrast, implantable time-release systems may help minimize peak plasma levels and reduce the risk of adverse reactions, allow for more predictable and extended duration of action, reduce the frequency of re-dosing and improve patient acceptance and compliance. Nano-implants will also be used in the not-too-distant future for treating cancer. Among the first nanoscale devices to show promise in anti-cancer therapeutics and drug delivery are structures called nanoshells, which NanoMarkets believes may afford a degree of control never before seen in implantable drug delivery products. There are some areas where nano-enhanced drugs could make a big difference in increasing oral bioavailability and reducing undesirable side effects. By increasing bioavailability, Nanoparticles can increase the yield in drug development and more importantly may help treat previously untreatable conditions [10].

NANOPARTICLE MECHANISM OF ACTION

Nanoparticle drug encapsulation offers several advantages in creating effective means of drug delivery and localization. Nanoparticle traits such as particle size, surface charge, and shape play important roles in creating effective Nanoparticle delivery systems that function through a variety of mechanisms.

1. Effect of Particle Size

Particle size can affect the efficiency, biodistribution and cellular uptake of various Nanoparticle systems [11]. It is thought that size parameters can play significant roles in the

determination of cell interaction and adhesion for various Nanoparticles. Size can also play an important part in the degradation and elimination processes of Nanoparticles. In certain Nanoparticle systems, the primary aim is to avoid the reticuloendothelial system that targets foreign bodies for degradation. Avoidance of this system increases in total blood circulation time and bioavailability. As such, it is important to note that Nanoparticle size has been directly correlated with clearance (CL). As the size of Nanoparticles increase, the rate of CL increases as well. It has been shown that Nanoparticles with hydrophilic surfaces exhibiting a particle size < 100 nm can effectively avoid the mononuclear phagocytic system (MPS). MPS is a critical element in physiological systems for the elimination of foreign substances. Blood serum contains opsonin proteins that can efficiently bind to larger Nanoparticles and tag them for MPS degradation [12]. Nanoparticles that obtain small particle diameter and hydrophilic properties can avoid opsonization and MPS degradation, thus enhancing total blood circulation time [11,12]. Nanometric particles can undergo extensive cellular uptake in comparison to micrometric particles [13]. In a study conducted by Desai et al., it was shown that Nanoparticle uptake of an in situ rat intestinal loop model demonstrated 15- to 250-fold increases in cellular uptake when compared with larger microparticles [14]. Another study showed positive particle size influence in regards to cellular and tissue uptake [15].

2. Effect of Particle Charge

Nanoparticle charge plays a critical role in the action and efficiency of Nanoparticle delivery to and through cellular membranes [16]. The stability of a Nanoparticle system is facilitated through the degree of surface charge present on Nanoparticles. A highly charged system undergoes a much larger degree of repulsion between like-charged particles. This net repulsive force acts to stabilize and prevent Nanoparticle aggregation. Nanoparticles formulated with more pronounced surface charges have been shown to stabilize Nanoparticle suspension and prevent particle aggregation. Surface charge characteristics can determine Nanoparticle's degree of absorption as it has been found that Nanoparticles with highly positive charges can interact with the anionic polyelectrolyte properties of mucus, resulting in enhanced mucoadhesion and retention of Nanoparticles within the mucus layer. Investigational studies performed with poly (lactic-co-glycolic acid) (PLGA) and polyvinyl alcohol formulated Nanoparticles have resulted in Nanoparticles with highly negative surface charges. Many cellular membranes are negatively charged. Nanoparticles formulated with known anionic polymers or surfactants will be presented with a higher net negative surface

charge. This increased negative surface charge will result in the repulsion of the Nanoparticle when it comes to the vicinity of cell membranes. As a result of this repulsive force, cellular uptake becomes difficult and cellular adhesion is reduced. Positively charged nanoparticles experience opposite effects. The cationic nanoparticle facilitates membrane attraction and adhesion, which creates favorable properties for cellular uptake via endocytosis or other mechanisms.

3. Effect of Particle Shape

In recent years, research has revealed that particle shape may have fundamental effects on the biological properties of Nanoparticles [17]. In a study conducted by Geng et al., it was found that polymer micelles of shorter stature showed an increased total blood circulation time following intravenous (i.v.) injection [18]. When compared to longer micelles, shorter spheres also underwent a higher degree of cell uptake and effectively delivered the drug, paclitaxel, to targeted tumor cells. Another study found that the length of Nanoparticle inversely influenced cellular adhesion [19]. In that study, it was found that as particle length increased the subsequent binding of Nanoparticles decreased, suggesting that attachment and adhesion is a function of cellular length. These studies suggest the importance of Nanoparticle shape in therapeutic outcomes about drug design and delivery. In Nanoparticle development, characterization and design must not only pertain to particle size or surface charge. Shape effects on targeted Nanoparticle outcomes must also be dually considered.

4. Cell Targeting

Many biological targets for nanomedicines are large complex molecules such as membrane receptors [20]. Biological processes are initiated through polyvalent interaction between these targeted receptors and their appropriate ligand. Many NP formulations have been developed that largely overlook NP valence capacitance and receptor interactions. However, some formulations such as dendrimer and polymer-based NPs have been documented to function through polyanionic receptor-mediated targeting [21]. Dendrimer-based NP systems have demonstrated targeted viral and cellular interactions via polyvalent interactions with varying surface proteins. Folate-formulated polymer-based NPs have been shown to bind to overexpressed folate receptors common to tumor cells and initiate cellular entry [20]. Other polymer-formulated NPs have shown specificity for caveolae and clathrin proteins resulting in endocytosis uptake via differing target mechanisms [22]. Polymeric micelles have

demonstrated the ability to target cancer cells and initiate cellular uptake while avoiding excess uptake in normal epithelial cells. This difference in cell type uptake is thought to be a result of NP differentiation of endocytosis mechanisms common to each cell type [21]. Carcinogenic cellular uptake is initiated through caveolae-mediated endocytosis, which is absent in normal cell lines. The caveolae targeting capacitance of polymeric micelles enables drug uptake into cancerous cell lines while avoiding drug uptake in normal cells. As a result, cytotoxic drugs can be formulated in polymer-based micelles for cancer treatment that could avoid cytotoxicity of normal functional cell types.

CHARACTERISTICS OF NANOPARTICLE FOR DRUG FORMULATIONS

There are the following characteristics of Nanoparticle for drug formulation:

1. Size of Particle

The particle size gets smaller, their surface area to volume ratio gets larger. This would imply that more of the drug is closer to the surface of the particle compared to a larger molecule. Being at or near the surface would lead to faster drug release [23]. Most importantly, Nanoparticles can cross the BBB providing sustained delivery of medication for diseases of CNS [24]. It would be beneficial to create Nanoparticle systems that have a large surface area to volume ratio; however, toxicity must always be monitored. As mentioned earlier, the size of the Nanoparticle determines biological fate. Remember that the vascular and lymph systems are responsible for the filtering and clearance of foreign matter and chemicals. This is yet another factor that must be engineered into the ideal Nanoparticle system. It has been shown that particles 200 nm or larger tend to activate the lymphatic system and are removed from circulation quicker [25]. Thus, it is clear as though the optimum size for a Nanoparticle is approximately 100 nm. At this size, the particle could pass through the BBB, sufficient amount of drug delivery due to the high surface area to volume ratio, and avoiding immediate clearance by the lymphatic system.

2. Surface Properties:

Hydrophobic Nanoparticles are cleared easily, it seems logical to assume that making their surface hydrophilic would increase their time in circulation. Coating the Nanoparticles with polymers or surfactants or creating copolymers like polyethylene glycol (PEG), diminishes the opsonization), polyethylene oxide, polyethylene glycol (prevents hepatic and splenic

localization), poloxamer, poloxamine, and polysorbate 80 has been proven valuable [26, 27]. PEG is a hydrophilic and relatively inert polymer that when incorporated in the Nanoparticle surface, hinders the binding of plasma proteins (opsonization), and thus preventing substantial loss of the given dose. PEGylated Nanoparticles are often referred to as ‘‘stealth” Nanoparticles because, without opsonization, they remain undetected by the reticuloendothelial system (RES) [28]. The surface of the particle must be large enough to avoid leakage into blood capillaries, but not too large to become susceptible to macrophage clearance. By manipulating the surface, the extent of aggregation and clearance can be controlled.

3. Drug Loading and Release

The size and surface properties of Nanoparticles have been explored to optimize the bioavailability, decrease clearance, and increase stability. The release of drugs from the Nanoparticle-based formulation depends on many factors including, pH, temperature, drug solubility, desorption of the surface-bound or adsorbed drug, drug diffusion through the Nanoparticle matrix, Nanoparticle matrix swelling and erosion, and the combination of erosion and diffusion processes [29, 30].

ADVANTAGES OF NANOPARTICLES IN DRUG DELIVERY SYSTEM

1. The allowable size of Nanoparticles to be administered intravenously, unlike the colloidal system which could occlude in blood capillaries and needle.

2. Due to its small size than microspheres and liposomes, they can easily pass through the sinusoidal spaces in the bone marrow and spleen as compared to other systems with long circulation time.

3. Due to their larger surface area, Nanoparticles have higher loading capacity.

4. Nanoparticles increase the stability of drugs/proteins against enzymatic degradation.

5. Nanoparticles are safe and effective in site-specific and targeted drug delivery systems.

6. To enhances the targeting moieties by adhering monoclonal antibodies with Nanoparticles for specificity.

7. It improves the solubility of poorly water-soluble drugs.

8. It improves bioavailability by reducing the fluctuations in the therapeutic ranges.

9. It reduces the toxicity of the liver.

10. They offer a significant improvement over traditional oral and intravenous methods of administration in terms of efficiency and effectiveness.

DRUG RELEASE FROM NANOPARTICLES

The Nanoparticle is coated by polymer, which releases the drug by controlled diffusion or erosion from the core across the polymeric membrane or matrix. The membrane coating acts as a barrier to release, therefore, the solubility and diffusivity of drug in the polymer membrane become the determining factor in drug release. Furthermore, the release rate can also be affected by the ionic interaction between the drug and the addition of auxiliary ingredients. When the drug is involved in the interaction with auxiliary ingredients to form a less water-soluble complex, then the drug release can be very slow with almost no burst release effect [31].

To develop a successful nanoparticulate system, both drug release and polymer biodegradation are important consideration factors. In general, drug release rate depends on (1) solubility of drug, (2) desorption of the surface-bound/ adsorbed drug, (3) drug diffusion through the Nanoparticle matrix, (4) Nanoparticle matrix erosion/degradation and (5) combination of erosion/diffusion process [32]. Thus solubility, diffusion, and biodegradation of the matrix materials govern the release process.

TYPES OF NANOPARTICLES AS CARRIER

The classes of Nanoparticles listed below are all very general and multi-functional; however, some of their basic properties and current known uses in nanomedicine are described here.

1. Fullerenes

A fullerene is any molecule composed entirely of carbon, in the form of a hollow sphere, ellipsoid, or tube. Spherical fullerenes are also called buckyballs, and cylindrical ones are called carbon nanotubes or buckytubes. Fullerenes are similar in structure to the graphite, which is composed of stacked graphene sheets of linked hexagonal rings, additionally, they

may also contain pentagonal (or sometimes heptagonal) rings to give potentially porous molecules [33]. Buckyball clusters or buckyballs composed of less than 300 carbon atoms are commonly known as endohedral fullerenes and include the most common fullerene, buckminsterfullerene, C60. Megatubes are larger in diameter than nanotubes and prepared with walls of different thickness which is potentially used for the transport of a variety of molecules of different sizes [34]. Nano ‘‘onions’’ are spherical particles based on multiple carbon layers surrounding a buckyball core which are proposed for lubricants [35].

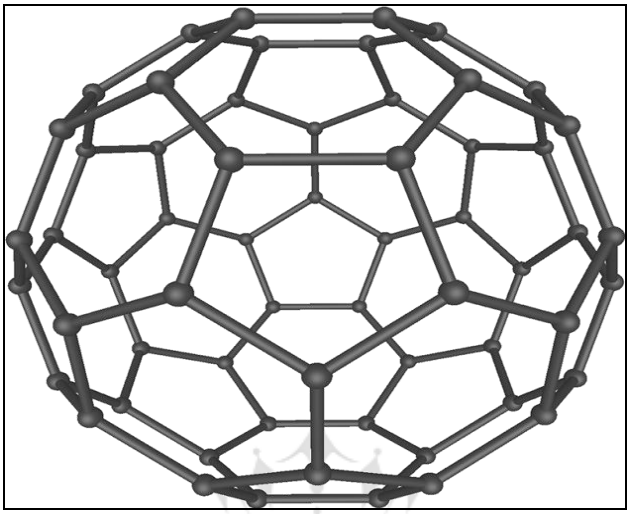

Figure 1: Structure of Fullerenes

2. Solid Lipid Nanoparticles (SLNs)

SLNs mainly comprise lipids that are in the solid phase at the room temperature and surfactants for emulsification, the mean diameters of which range from 50 nm to 1000 nm for colloid drug delivery applications [36]. SLNs offer unique properties such as small size, large surface area, high drug loading, the interaction of phases at the interfaces, and are attractive for their potential to improve the performance of pharmaceuticals, nutraceuticals and other materials [37]. The typical methods of preparing SLNs include spray drying [38], high shear mixing [39], ultra-sonication [40, 41], and high-pressure homogenization (HPH) [42, 43]. Solid lipids utilized in SLN formulations include fatty acids (e.g. palmitic acid, decanoic acid, and behenic acid), triglycerides (e.g. trilaurin, trimyristin, and tripalmitin), steroids (e.g. cholesterol), partial glycerides (e.g. glyceryl monostearate and glyceryl behenate) and waxes (e.g. cetyl palmitate). Several types of surfactants are commonly used as emulsifiers to stabilize lipid dispersion, including soybean lecithin, phosphatidylcholine, poloxamer 188, sodium cholate, and sodium glycocholate [44].

The advantages of these solid lipid Nanoparticles (SLN) are the use of physiological lipids, the avoidance of organic solvents in the preparation process, and a wide potential application spectrum (dermal, oral, intravenous). Additionally, improved bioavailability, protection of sensitive drug molecules from the environment (water, light) and controlled and/or targeted drug release [45-47], improved stability of pharmaceuticals, feasibilities of carrying both lipophilic and hydrophilic drugs and most lipids being biodegradable [48, 49].

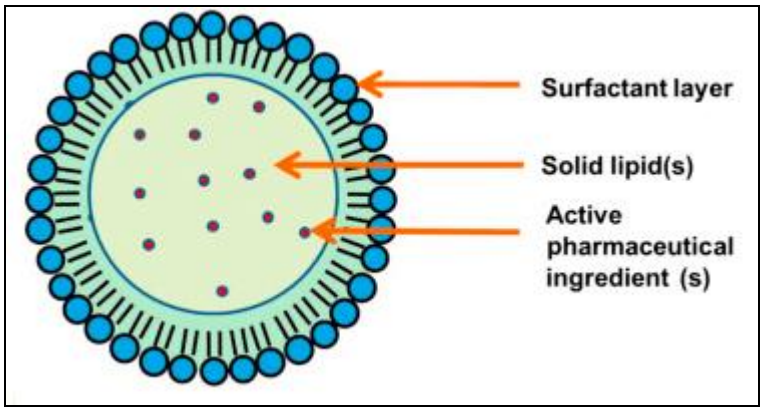

Figure 2: Structure of Solid Lipid Nanoparticles

3. Liposomes

Liposomes are vesicular structures with an aqueous core surrounded by a hydrophobic lipid bilayer, created by the extrusion of phospholipids. Phospholipids are GRAS (generally recognized as safe) ingredients, therefore minimizing the potential for adverse effects. Solutes, such as drugs, in the core, cannot pass through the hydrophobic bilayer however hydrophobic molecules can be absorbed into the bilayer, enabling the liposome to carry both hydrophilic and hydrophobic molecules. The lipid bilayer of liposomes can fuse with other bilayers such as the cell membrane, which promotes the release of its contents, making them useful for drug delivery and cosmetic delivery applications. Liposomes that have vesicles in the range of nanometers are also called nanoliposomes [50, 51]. Liposomes can vary in size, from 15 nm up to several lm and can have either a single layer (unilamellar) or multiple phospholipid bilayer membranes (multilamellar) structure. Unilamellar vesicles (ULVs) can be further classified into small unilamellar vesicles (SUVs) and large unilamellar vesicles (LUVs) depending on their size range [52]. The unique structure of liposomes, a lipid membrane surrounding an aqueous cavity, enables them to carry both hydrophobic and hydrophilic compounds without chemical modification. Also, the liposome surface can be

easily functionalized with 'stealth' material to enhance their in vivo stability or targeting ligands to enable preferential delivery of liposomes.

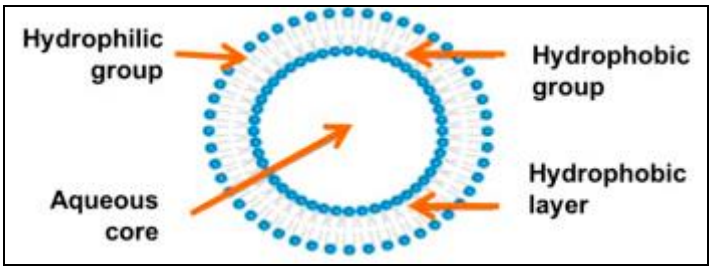

Figure 3: Structure of Liposome

4. Nanostructured Lipid Carriers (NLC)

Nanostructured Lipid Carriers are produced from a blend of solid and liquid lipids, but particles are in solid-state at body temperature. Lipids are versatile molecules that may form differently structured solid matrices, such as the nanostructured lipid carriers (NLC) and the lipid drug conjugate Nanoparticles (LDC), that have been created to improve drug loading capacity [53]. The NLC production is based on solidified emulsion (dispersed phase) technologies. NLC can present an insufficient loading capacity due to drug expulsion after polymorphic transition during storage, particularly if the lipid matrix consists of similar molecules. Drug release from lipid particles occurs by diffusion and simultaneously by lipid particle degradation in the body. In some cases, it might be desirable to have a controlled fast release going beyond diffusion and degradation. Ideally, this release should be triggered by an impulse when the particles are administered. NLCs accommodate the drug because of their highly unordered lipid structures. A desired burst drug release can be initiated by applying the trigger impulse to the matrix to convert in a more ordered structure. NLCs of certain structures can be triggered this way [54].

NLCs can generally be applied where solid Nanoparticles possess advantages for the delivery of drugs. Major application areas in pharmaceutics are topical drug delivery, oral and parenteral (subcutaneous or intramuscular and intravenous) route. LDC Nanoparticles have proved particularly useful for targeting water-soluble drug administration. They also have applications in cosmetics, food and agricultural products.

These have been utilized in the delivery of anti-inflammatory compounds, cosmetic preparation, topical cortico therapy and also increases bioavailability and drug loading capacity.

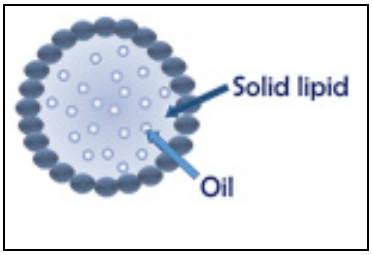

Figure 4: Structure of Nanostructured Lipid Carriers

5. Nanoshells

Nanoshells are also notorious as core-shells, nanoshells are spherical cores of a particular compound (concentric particles) surrounded by a shell or outer coating of a thin layer of another material, which is a few 1–20 nm nanometers thick. Nanoshell particles are highly functional materials that show modified and improved properties than their single-component counterparts or Nanoparticles of the same size. Their properties can be modified by changing either the constituting materials or core-to-shell ratio [55]. Nanoshell materials can be synthesized from semiconductors (dielectric materials such as silica and polystyrene), metals and insulators. Usually, dielectric materials such as silica and polystyrene are commonly used as a core because they are highly stable [56]. Metal nanoshells are a novel type of composite spherical Nanoparticles consisting of a dielectric core covered by a thin metallic shell which is typically gold. Nanoshells possess highly favorable optical and chemical properties for biomedical imaging and therapeutic applications. Nanoshells offer other advantages over conventional organic dyes including improved optical properties and reduced susceptibility to chemical/thermal denaturation. Furthermore, the same conjugation protocols used to bind biomolecules to gold colloids are easily modified for nanoshells [57]. When a nanoshell and polymer matrix is illuminated with resonant wavelength, nanoshells absorb heat and transfer to the local environment. This causes the collapse of the network and the release of the drug. In core-shell particles-based drug delivery systems either the drug can be encapsulated or adsorbed onto the shell surface [58]. The shell interacts with the drug via a specific functional group or by electrostatic stabilization method. When it comes in contact with the biological system, it directs the drug. In imaging applications, nanoshells can be tagged with specific

antibodies for diseased tissues or tumors. Nanoshell materials have received considerable attention in recent years because of potential applications associated with them.

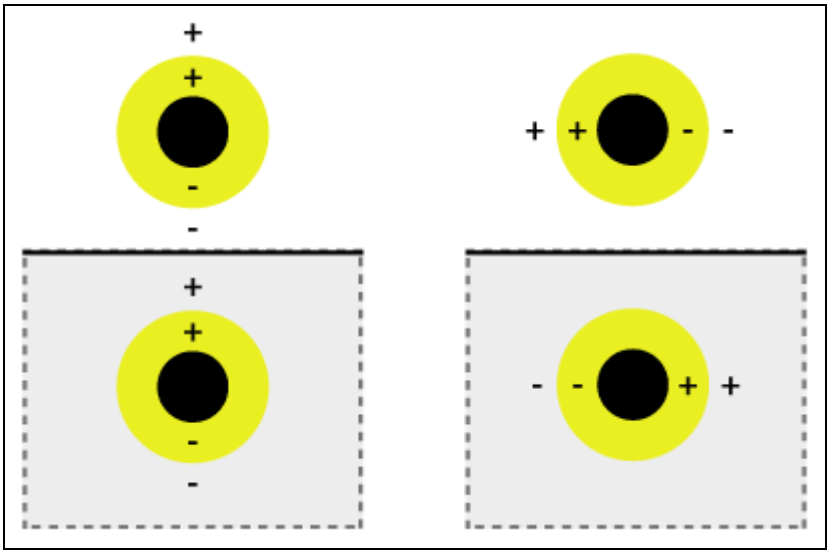

Figure 5: Structure of Nanoshell

6. Quantum Dots (QD)

The quantum dots are semiconductor nanocrystals and core-shell nanocrystals containing interface between different semiconductor materials. The size of quantum dots can be continuously tuned from 2 to 10 nm, which, after polymer encapsulation, generally increases to 5–20 nm in diameter. Particles smaller than 5 nm are quickly cleared by renal filtration [59]. Semiconductor nanocrystals have unique and fascinating optical properties, become an indispensable tool in biomedical research, especially for multiplexed, quantitative and long-term fluorescence imaging and detection [60-63]. QD core can serve as the structural scaffold, and the imaging contrast agent and small molecule hydrophobic drugs can be embedded between the inorganic core and the amphiphilic polymer coating layer. Hydrophilic therapeutic agents including small interfering RNA (siRNA) and antisense oligodeoxynucleotide (ODN) and targeting biomolecules such as antibodies, peptides and aptamers can be immobilized onto the hydrophilic side of the amphiphilic polymer via either covalent or non-covalent bonds. This fully integrated nanostructure may behave like magic bullets that will not only identify but bind to diseased cells and treat it. It will also emit detectable signals for real-time monitoring of its trajectory [64].

7. Superparamagnetic Nanoparticles

Superparamagnetic molecules are those that are attracted to a magnetic field but do not retain residual magnetism after the field is removed. Nanoparticles of iron oxide with diameters in the 5–100 nm range have been used for selective magnetic bioseparations. Typical techniques involve coating the particles with antibodies to cell-specific antigens, for separation from the surrounding matrix. The main advantages of superparamagnetic Nanoparticles are that they can be visualized in magnetic resonance imaging (MRI) due to their paramagnetic properties; they can be guided to a location by the use of magnetic field and heated by a magnetic field to trigger the drug release [65]. Superparamagnetic Nanoparticles belong to the class of inorganic based particles having an iron oxide core coated by either inorganic materials (silica, gold) and organic (phospholipids, fatty acids, polysaccharides, peptides or other surfactants and polymers) [66-68]. In contrast to other Nanoparticles, superparamagnetic Nanoparticles based on their inducible magnetization, their magnetic properties allow them to be directed to a defined location or heated in the presence of an externally applied AC magnetic field. These characteristics make them attractive for many applications, ranging from various separation techniques and contrast-enhancing agents for MRI to drug delivery systems, magnetic hyperthermia (local heat source in the case of tumor therapy), and magnetically assisted transfection of cells [69-72].

8. Dendrimers

Dendrimers are unimolecular, monodisperse, micellar nanostructures, around 20 nm in size, with a well-defined, regularly branched symmetrical structure and a high density of functional end groups at their periphery. The structure of dendrimers consists of three distinct architectural regions as a focal moiety or a core, layers of branched repeat units emerging from the core, and functional end groups on the outer layer of repeat units. They are known to be robust, covalently fixed, three-dimensional structures possessing both a solvent-filled interior core (nanoscale container) as well as a homogenous, mathematically defined, exterior surface functionality [73-74].

Dendrimers are generally prepared using either a divergent method or a convergent one with architecture like a tree branching out from a central point. Dendrimeric vectors are most commonly used as parenteral injections, either directly into the tumor tissue or intravenously for systemic delivery [75]. Dendrimers used in drug delivery studies typically incorporate one

or more of the following polymers: polyamidoamine (PAMAM), melamine, poly L-glutamic acid (PG), polyethyleneimine (PEI), polypropylene imine (PPI), and polyethylene glycol (PEG), Chitin. Dendrimers may be used in two major modalities for targeting vectors for diagnostic imaging, drug delivery, gene transfection also detection and treatment of cancer and other diseases, namely by (1) passive targeting nano dimensions mediated via EPR (enhanced permeability retention) effect involving primary tumor vascularization or organ-specific targeting and (2) active targeting-receptor-mediated cell-specific targeting involving receptor-specific targeting groups [76].

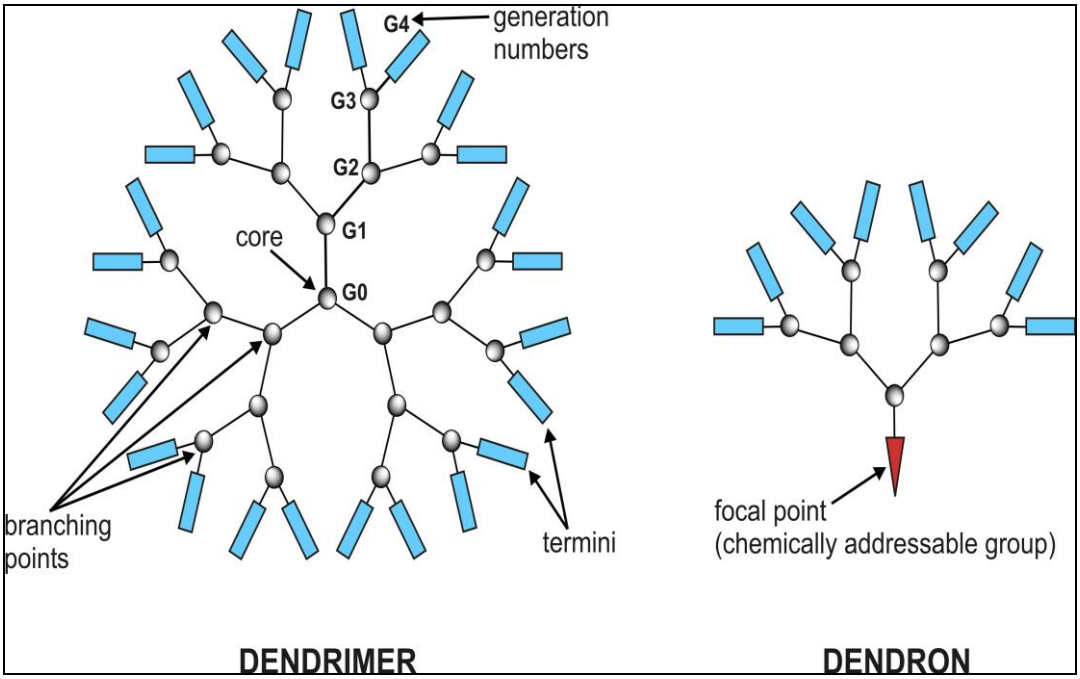

Figure 6: Structure of Dendrimer

APPLICATION OF NANOPARTICLE

1. Cancer Therapy

The type of therapy used to treat cancer patients today has saved the lives of man individuals; however, the side effects of treatment are harsh, affecting the entire body due to the non-specificity of the chemotherapeutic agents. Cancer is a very complicated biological phenomenon and can be considered a disease of many diseases. One of the hallmarks of cancerous cells is that they divide and multiply rapidly and out of control [77]. Current chemotherapy is mainly aimed at destroying all rapidly dividing cells. The downside of this therapy is that the body's other rapidly proliferating cells, such as in the hair follicles and

intestinal epithelium are also killed off, leaving the patient to cope with the life-altering side effects [78]. The development of Nanoparticles has provided a new avenue for chemotherapy. With smartly designed Nanoparticles, targeted drug delivery at the tumor site or a certain group of cells do largely avoid the toxic effects to other normal tissues and organs [79-80]. There have been several systems tested to provide this type of therapy.

Micelles and liposomes offer another option for the delivery of chemotherapeutic agents. Additionally, micelles are also a great way to make insoluble drugs soluble due to their hydrophobic core and a hydrophilic shell. If the micelle's surface is further PEGylated, it increases the ability of the nanocarriers to get through fenestrated vasculature of tumors and inflamed tissue through passive transport, thus resulting in higher drug concentration in tumors. As of now, several polymeric micelles containing anticancer drugs, NK012, NK105, NK911, NC-6004, and SP1049C are under clinical trials [81] and one such system, Genexol-PM (paclitaxel) is approved for breast cancer patients [82].

Dendrimers are highly branched macromolecules with many functional groups available for the attachment of drug, targeting and imaging agents and their absorption, distribution, metabolism, and elimination (ADME) profile is dependent upon various structural features [83, 84]. A polyfunctional dendrimer system has been reported for successful localization (Folic acid), imaging (fluorescein) and delivery of the anticancer drug methotrexate in vitro[85]. Nanoparticle therapeutics based on dendrimers can improve the therapeutic index of cytotoxic drugs by employing biocompatible components, and the surface derivatization with PEGylation, acetylation, glycosylation, and various amino acids [86-87]. While several other forms of Nanoparticles have shown promise in cancer treatment, one of the most recent systems is the carbon nanotubes. Carbon nanotubes (CNTs) are an allotropic form of carbon with the cylindrical framework and deepening on the number of sheets in concentric cylinders, they can be classified as single-walled carbon nanotubes (SWCNTs) and multiwalled carbon nanotubes (MWCNTs) [88-89]. Since Carbon nanotubes have a very hydrophobic hollow interior, water-insoluble drugs can easily be loaded. The large surface area allows for outer surface functionalization and can be done specifically for a particular cancer receptor as well as contrast agents [90].

2. Diagnostic Testing

The use of Nanoparticle for diagnostic purposes is an area that currently unavailable for clinical application but heavily explored in academia [91]. Since current technology for diagnostic testing is hindered by the inadequacies of fluorescent markers including fading of fluorescence after a single-use, color matching, and restricted use of dyes due to a bleeding effect, fluorescent Nanoparticles provide researchers with the answer to overcome these disadvantages [92]. One important breakthrough was the discovery of quantum dots which can be custom-made in many sharply defined colors. Their absorption spectrum ranges from UV to a wavelength within the visible spectrum and provides high quantum yield, tunable emission spectrum, and photostability. The size of the nanodot determines where in the spectra that individual particle falls. Larger particles have longer wavelengths and emission is narrow [93-95]. The tagging of the quantum dots has several advantages. First, they are excitable using white light. Secondly, they can be linked to biomolecules that can spend a considerable amount of time in the living system to probe various bio-mechanisms. This technology further allows one to monitor many biological events simultaneously by tagging various biological molecules with nanodots of a specific color [96].

Recently, theranostic Nanoparticles, Nanoparticles that can be used for treatment as well as diagnoses have gained much attention [97]. This strategy has been realized in many classes of Nanoparticles including, drug conjugates, dendrimers, surfactant aggregates (micelles and vesicles), core-shell particles, and carbon nanotubes. By combing both drug and imaging agents in one smart formulation various, it is possible to monitor the pathway and localization of this Nanoparticle at the target site as well as drug action to assess therapeutic response [98].

3. HIV And AIDS Treatment

Infection with human immunodeficiency virus (HIV), if not addressed can lead to acquired immune deficiency syndrome (AIDS) is a devastating disease where an individual's immune system is almost destroyed [99]. When treatment was first developed for this disease, it was painstakingly involved, where most patients could be taking 30–40 pills a day. In the past decade, there have been advancements in therapeutics to reduce the pill count down to just a few each day. Research has shown a way to make this therapy even more effective by creating polymeric Nanoparticles that deliver antiretroviral (ARV) drugs intracellularly as well as to the brain [100]. This technology can also be used in adjunct with vaccinations to

prevent HIV infections [101]. Antiretroviral drugs that are used to treat HIV, can be categorized depending on the stages of the HIV life cycle they work most suitably on. To prevent the development of resistance and aggressively counter the HIV progression, a combination of multiple drugs (three or more) is used, known as highly effective antiretroviral therapy (HAART) [102]. Nanotechnology has played a pivotal role in delivering antiretroviral drugs and improving compliance [103].

Antiretroviral drugs must be able to cross the mucosal epithelial barrier when taken orally or other non-parental routes (suppository and patches, etc.). Lymphoid tissues are major sites for HIV to infect and thrive. Several reports have demonstrated that Nanoparticle loaded with antiretroviral drugs were able to target monocytes and macrophages in vitro [104-105]. A prime example of superiority and success of the Nanoparticle system for sustained and targeted drug delivery was reported by Destache et al. (2009) [106]. The investigators used poly(lactic-co-glycolic acid) (PLGA) to prepare Nanoparticles entrapping three antiretroviral drugs, ritonavir, lopinavir, and efavirenz. The Nanoparticle system yielded sustained drug release for over 4 weeks (28 days), while free drugs were eliminated within 48 h (2 days). The Central nervous system (CNS) is another site for HIV to inoculate and thrive resulting in serious HIV associated neurocognitive disorder (HAND). Nanoparticles are known to be able to cross BBB by endocytosis/ phagocytosis and many reports exist showing successful delivery of anti-HIV medications [107-108].

4. Nutraceutical Delivery

Nutraceuticals are food-derived, standardized components with noticeable health benefits. They are commonly consumed as to complement various allopathic treatments as well as to provide extra health benefits and decrease risks of several chronic illnesses [109]. Similar to the case of any other drug, the bioavailability and thus the efficacy of orally consumed nutraceuticals is affected by food matrices interactions, aqueous solubility, degradation/ metabolism, and epithelial permeability [110]. Most nutraceuticals are lipophilic molecules, such as fat-soluble vitamins (A, D, E, and K), polyunsaturated lipids and other phytochemicals. Nanotechnology again offers comprehensive assistance and most of the investigations have been aimed at improving the dissolution mechanisms of nutraceuticals via Nanoparticle formulations [110-111]. A large number of nutraceuticals, posse anti-inflammatory, antioxidative, antiapoptotic, and antiangiogenic activities, among those, the most prominent and studied is curcumin (diferuloylmethane). It is practically water-insoluble and has very

poor bioavailability, thus various methods have been implemented to address this issue, such as liposomes, phospholipid vesicles, and polymer-based nano-formulation [112-113]. A 9-fold higher oral bioavailability of curcumin was observed when compared to curcumin co-administered with piperine (absorption enhancer) [114]. Another study of colloidal Nanoparticles of curcumin dubbed, Theracurmin when compared to curcumin powder, exhibited a 40-fold higher area under the curve (AUC) in rats and 27-fold higher in healthy human volunteers as well as inhibitory actions against alcohol intoxication [115].

Resveratrol is an important non-flavonoid polyphenol, naturally occurs in several plants but most abundantly found in Vitis vinifera, labrusca, and muscadine grapes [116]. It is known for antioxidant, cardioprotective, anti-inflammatory and anticancer activities [117]. Resveratrol has low solubility, with decent bioavailability, however, it is rapidly metabolized and eliminated from the body. There are two geometric isomers of resveratrol (cis- and trans), however, the more abundant and bioactive trans-resveratrol, is photosensitive, converters to cis-resveratrol in the presence of light [118]. Many nanoformulations of resveratrol to improve the pharmacokinetic profile and bioavailability have been reported. These include polymeric Nanoparticles, Zein based Nanoparticles, nanoemulsions, liposomes, cyclodextrins, and dual nanoencapsulation methods. Recently, the neuroprotective effects of resveratrol were evaluated by preparing solid lipid Nanoparticles decorated with apolipoprotein E for LDL receptor recognition on the blood-brain barrier [119].

5. Nanoparticles in Dermatology

Recent advances in the field of nanotechnology have allowed the manufacturing of elaborated nanometer-sized particles for various biomedical applications. Controlled drug release to the skin and skin appendages, targeting of hair follicle-specific cell populations, transcutaneous vaccination and transdermal gene therapy are only a few of these new applications. Carrier systems of the new generation take advantage of improved skin penetration properties, depot effect with sustained drug release and surface functionalization (e.g., the binding to specific ligands) allowing specific cellular and subcellular targeting. Drug delivery to the skin using microparticles and nanocarriers could revolutionize the treatment of several skin disorders [120].

Dermal drug delivery with (lipid Nanoparticle) LN is of particular interest for diseases of the HF (hair follicle) to increase the local bioavailability of API at their drug target. Several targets were identified for drugs in the HF; for instance, isotretinoin causes a cell cycle arrest

and apoptosis in sebocytes, minoxidil stimulates the vascular endothelial growth factor and prostaglandin synthesis in the dermal papilla [121] and cyclosporine A supports hair epithelial cell growth [122]. In dermal therapy, the main goal is to circumvent systemic adverse effects by local administration of the API. Generally, severe disease states are treated systemically; therefore, one main unmet medical need remains effective topical targeting. In general, follicular targeting remains one of the most promising concepts in current topical drug delivery applications apart from epidermal penetration and manipulation of SC lipid organization [123].

The smallest particle sizes are observed for SLN dispersions with low lipid content (up to 5%). Both the low concentration of the dispersed lipid and the low viscosity is disadvantageous for dermal administration. In most cases, the incorporation of the SLN dispersion in an ointment or gel is necessary to achieve a formulation that can be administered to the skin. The incorporation step implies a further reduction of the lipid content. An increase of the solid lipid content of the SLN dispersion results in semisolid, gel-like systems, which might be acceptable for direct application on the skin. In general, alternative dosage forms to transdermal therapeutics systems are hard to establish due to a limited permeation rate which also applies to LN. Prospective approaches that are in the focus of research are the introduction of enhancers, iontophoresis, and microneedles which are all invasive [124].

CONCLUSION

The nanoparticle is essentially a multidisciplinary science in which chemists, physicists, biologists, and pharmaceutical scientists have played major roles in developing new modalities for treatment and diagnosis. Through this study, it is clear that the implementation of no nanoparticular in drug delivery and medication has paved new paths and opened several doors to provide flexible and healthier treatment options. With the introduction of nanoparticles, the treatment of cancer and HIV / AIDS, non-invasive imaging and nutraceutical delivery have all improved. Finally, by controlling the molecular size and surface properties, researchers can deliver drugs with less frequent dosing (sustained-release) for a longer period and with greater precision and penetration in tissue that is difficult to access. There is a wide range of nanoparticulate materials and structures being developed for the delivery of therapeutic compounds. Each has its unique advantages, but as these nanoparticles are tailored for their specific application, as a result of targeted delivery of

smaller amounts of effective drugs to the appropriate locations in the body, the result will be better-controlled therapy. This is made possible by using advanced technology, enhanced particle size regulation, and a better understanding of the interaction between the biological and material surfaces, and their *in-vivo* effects. Some products based on nanoparticles are already licensed by the US FDA, and a variety of others are currently under development and clinical evaluation.

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