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NANOCARRIER: AS AN APPROACH OF DRUG DELIVERY SYSTEM

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ABSTRACT

Development of new delivery systems that deliver the potential drug specifically to the target site in order to meet the therapeutic needs of the patients at the required time and level remains the key challenge in the field of pharmaceutical technology. Nanoscience is concerned with the study of the unique properties of matter at its nano level and exploits them to create novel structures, devices and systems for a variety of different uses. This review highlights the different types of nanoparticulate delivery systems employed for drugs in the field of molecular medicine with a short overlook at its applications.

1. Introduction:

The word **nano** is derived from the Greek word for "dwarf". Nanoscience is concerned with the study of the unique properties of matter at its nano level and exploits them to create novel structures, devices and systems for a variety of different uses. Particles having sizes less than 100 nm are generally called nanoparticles. These have strikingly different properties due to their small size and thus are found useful in many applications. The ability to measure and manipulate matter on the nanometer level is making possible a new generation of materials with enhanced mechanical, optical, transport and magnetic properties. Nanocarriers are materials or devices of nanoscale (below 1μm) made up of different biodegradable materials like natural or synthetic polymers, lipids or phospholipids and even organometallic compounds, which delivered of drug to various sites within the body – as well as in non-living systems – and their release behavior is directly affected by particle size. [1] The protection of bioactive agents, including drugs, vaccines, nutrients and cosmetics, from degradation and inactivation has been investigated extensively using microencapsulation systems. However, to provide targeted controlled release is a key functionality that can be provided much more efficiently by employing nanocarrier technologies. Advancements in nanoscience and technology have made it possible to manufacture and analyze sub-micrometric drug carriers (Nanocarriers) on a routine basis. [2]

2. Comparison between micrometer size carriers and Nanocarrier:

Compared to micrometer size carriers, nanocarriers provide more surface area and have the potential to increase solubility, enhance bioavailability, improve controlled release and enable precision targeting of the entrapped compounds to a greater extent. As a consequence of improved stability and targeting, the amount of material required to exert a specific effect when encapsulated or incorporated to Nanocarrier is much less than the amount required when unencapsulated. This is particularly useful when dealing with expensive drug materials. A timely and targeted release improves the effectiveness of drugs, broadens their application range and ensures optimal dosage, thereby improving cost-effectiveness of the product. Reactive or sensitive material, such as polynucleotide's and polypeptides, can be turned into stable ingredients through encapsulation or entrapment by nanocarrier systems. It is also possible to prepare multireservoir nanocarriers in which two or more material are segregated in different compartments of the same capsule, minimizing their contact and undesired interactions while releasing them at the target site simultaneously. [2]

3. The functionalities of nanocarriers are expected to provide:

(a) Prolonged circulation in the blood and the ability to accumulate in various pathological areas (such as solid tumors) via the EPR (Enhanced Permeability and Retention) effect (protective polymeric coating with PEG is used for this purpose). [3]

(b) Ability to specifically recognize and bind target tissues or cells via the surface-attached specific ligand (monoclonal antibodies as well as their Fab fragments and some other molecules are used for this purpose). [4]

(c) Ability to respond local stimuli characteristic of the pathological site by releasing an entrapped drug or specifically acting on cellular membranes under the abnormal pH or temperature in disease sites (this property could be provided by surface attached pH- or temperature-sensitive coatings).

(d) Ability to penetrate inside cells bypassing the lysosomal degradation for efficient targeting of intracellular drug targets (for this purpose, the surface of nanocarriers may be decorated by cell-penetrating peptides).

4. Types of Nanocarrier:

Nanocarriers or Nano drug delivery systems (NDDS) are a sub-class of advanced drug delivery systems that consists of drug carriers with a size of less than one micrometer and mostly less than 200 nm. Examples for Nanocarriers are liposomes, nanosuspensions, polymeric nanoparticles, dendrimers, fullerenes, carbon nanotubes, and inorganic nanoparticles etc.

4.1 Polymeric nanoparticles:

Nanoparticles are sub-nanosized colloidal structures composed of synthetic or semi-synthetic polymers that vary in size from 10—1000 nm. The most active area of research using polymeric nanoparticles is in controlled delivery of pharmaceuticals following parenteral, oral, pulmonary, nasal, and topical routes of administration. [5] The drug of interest is either dissolved, entrapped, adsorbed, attached or encapsulated into the nanoparticle matrix. Polymeric materials exhibit several desirable properties including biocompatibility, biodegradability, surface modification, and ease of functionalization of polymers. Polymeric systems allow for a greater control of pharmacokinetic behavior of the loaded drug, leading to more appropriate steady levels of drugs. These attributes make it a candidate system for effective entrapment or encapsulation of biotech drugs that are usually sensitive to the changes in the surroundings. The most broadly investigated polymers include the natural chitosan, alginate, gelatin and albumin and the synthetic polylactic acid (PLA), poly(lactic-co-glycolic) acid (PLGA), polycaprolactone (PCL), poly(cyanoacrylate) (PCA), poly (methacrylic acid-co-ethylacrylate) block copolymer as well as combinations with other materials such as poly(ethylene glycol) (PEG). [6]

4.2 Ceramic nanoparticles:

The newly emerging area of using inorganic (ceramic) particles with entrapped biomolecules has potential applications in many frontiers of modern material science including drug delivery. [7] This type of system is called Ceramic nanoparticle. Such inorganic (ceramic) particles, including

silica, alumina, titania etc. are known for their compatibility with biological systems. [8] Ceramic nanoparticles have several advantages such as the preparative processes are relatively similar to the well-known sol-gel process, require ambient temperature condition, and can be easily prepared with the desired size, shape and porosity. Their ultra-low size (less than 50 nm) can help them evade by the reticulo-endothelial system (RES) of the body. In addition, there are no swelling or porosity changes with change in pH. These particles effectively protect doped molecules (enzymes, drugs, etc) against denaturation induced by external pH and temperature. Their surfaces can be easily modified with different functional groups. Therefore, they can be conjugated to a variety of monoclonal antibodies or ligands to target them to desired sites in vivo. [9]

4.3 Polymeric micelles:

Polymeric micelles are nano-structures formed by the self-assembly of amphiphiles in water, above a minimal concentration called the critical micelle concentration or CMC. Polymeric micelles are composed by internal and external zones named core and shell, respectively. The most developed amphiphilic block copolymers assemble into spherical core-shell micelles approximately 10 to 80 nm in diameter, consisting of a hydrophobic core for drug loading and a hydrophilic shell that acts as a physical ("steric") barrier to both micelle aggregation in solution, and to protein binding and opsonization during systemic administration. [10]

The most common hydrophilic block used to form the hydrophilic shell is the FDA-approved excepient poly (ethylene glycol) (PEG) or poly(ethylene oxide) (PEO). Unlike the hydrophilic block, which is typically PEG or PEO, different types of hydrophobic blocks have been sufficiently developed as hydrophobic drug loading cores. Examples of **Di-block copolymers** include: **(a)** poly(L-amino acids), **(b)** biodegradable poly(esters), which includes poly(glycolic acid), poly(D lactic acid), poly(D,L-lactic acid), copolymers of lactide/glycolide, and poly(ecaprolactone), **(c)** phospholipids/long chain fatty acids, and for **Tri-block copolymers**, **(d)** polypropylene oxide (in Pluronics/poloxamers). The choice of hydrophobic block is largely dictated by drug compatibility with the hydrophobic core (when drug is physically loaded) and the kinetic stability of the micelle. [11]

Polymer micelles have been extensively studied as drug carriers. Conjugating to ligands such as antibodies can enhance targeting potential of micelles. Immunomicelles is one such novel approach in which antibody conjugated polymeric micelles containing ant tumor drug Taxol was prepared and results demonstrated effective delivery at tumor site. Targeting has also been achieved in other drugs with reduced toxicity. Novel polymeric micelles with target ability and stimuli sensitivity have emerged as promising carriers in gene and drug delivery, and can potentially establish landmarks in the future of drug delivery systems. [12]

4.4 Lipid-based nanoparticles:

4.4.1 Liposome:

The first suggested use of liposome's came from the group of Weismann in 1969, since than liposome has been used as a versatile tool in biology, biochemistry and medicine. Liposomes are concentric bilayered vesicles in which an aqueous volume is entirely enclosed by a membranous lipid bilayer mainly composed of natural or synthetic phospholipids. Because of their size, hydrophobic and hydrophilic character, as well as biocompatibility, liposome are promising systems for drug delivery. Liposome properties vary substantially with lipid composition, size, surface charge and the method of preparation. Therefore they are classified into three classes based on their size and number of bilayers. Small unilamellar vesicles (SUV) are surrounded by a single lipid layer and are 25–50 nm in diameter. Large unilamellar vesicles (LUV) are a heterogeneous group of vesicles similar to SUVs and are surrounded by a single lipid layer. Multilamellar vesicles (MLV), however, consist of several lipid layers separated from one another by a layer of aqueous solution. [13]

4.4.2 Solid Lipid Nanoparticles (SLN):

Solid lipids have been used for several years in the form of pellets in order to achieve a retarded drug release after per oral administration (e.g. Mucosolvan Retard Capsules). In the beginning of the 80s, Speiser and coworkers developed solid lipid microparticles (by spray drying) and 'Nanopellets for per oral administration'. [14]At the beginning of the 90s the new generation has been developed the so-called "solid lipid nanoparticles" (SLN). SLN particles made from solid lipids are submicron colloidal carriers (50—1000 nm) dispersed either in water or in aqueous surfactant solution General ingredients include solid lipid(s), emulsifier(s) and water. The term lipid is used here in a broader sense and includes triglycerides (e.g. triemulsifierstearin), partial glycerides (e.g. Imwitor), fatty acids (e.g. stearic acid), and steroids (e.g. cholesterol) and waxes (e.g. cetyl palmitate). All classes of emulsifiers (with respect to charge and molecular weight) have been used to stabilize the lipid dispersion. In particular poloxamer 188, polysorbate 80, lecithin, polyglycerol, methyl glucose, distearate, sodium cocoamphoacetate or saccharose fatty acid esters are very often employed. It has been found that the combination of emulsifiers might prevent particle agglomeration more efficiently. SLN are prepared by various techniques such as high-pressure homogenization, microemulsion formation, precipitation, and as lipid nanopellets and lipospheres. [15]

The SLN combine the advantages of other innovative carrier systems (e.g. physical stability, protection of incorporated labile drugs from degradation, controlled release, excellent tolerability) while at the same time minimizing the associated problems. Another clear advantage of SLN compared to polymeric nanoparticles is the availability of large scale production units.

SLN formulations for various application routes (parenteral, oral, dermal, ocular, pulmonary and rectal) have been developed and thoroughly characterized in vitro and in vivo. [16]

4.5 Dendrimer:

The word dendrimer is derived from the Greek words dendri- (tree branch-like) and meros (part of), and the synthesis of 'true dendrimers' was achieved by Tomalia group (Dow Chemical Co.) about 20 years ago. Dendrimers are considered as highly branched macromolecules; they are small in size, while their low polydispersity can contribute to the reproducibility of their pharmacokinetic behavior. An ideal dendrimer as drug delivery system must be non-toxic, non-immunogenic and biodegradable. The First complete dendrimer family which has been synthesized, characterized and commercialized is the polyamidoamine (PAMAM) dendrimer. Dendrimer are also made up of different types of other polymers such as poly (L-glutamic acid), polyethylene mine, polypropylene mine, and polyethylene glycol. A typical dendrimer consists of a core, the branches and the surface groups. Dendrimers - due to their small size, low polydispersity and complete control of their structure - provide some special advantages for drug delivery. These include the prolongation of the drug in the circulation, the protection of the drug from its environment, the increase of the stability and, possibly, effectiveness of the drug and the capability of targeting to specific tissues. [17]

4.6 Nanocrystal and Nanosuspension:

Investigations in drug delivery research are directed with defined emphasis on drug solubility problems and their redressal. Typical problems associate with poorly soluble drug are low bioavailability and erractic absorption (oral administration) and problems of preparing parenteral dosage forms. To overcome these problems introduced two new aspects such are nanocrystals and nanosuspensions. Nanocrystals are aggregates of around hundreds or thousands of molecules that combine in a crystalline form, composed of pure drug with only a thin coating comprised of surfactant or combination of surfactants. The production technique of nanocrystals is known as 'nanonisation'. Dispersion of drug nanocrystals in liquid media leads to "nanosuspensions". [18]

4.7 Cells and Cell Ghosts Nanocarrier:

Microparticle and nanoparticle polymeric systems currently occupy an important place in the field of drug delivery and targeting. Nevertheless, there are biological drug carriers that offer an efficient alternative to such systems. Within the different systems of biological carriers, of great importance are cells and cell ghosts, which are both efficient and highly compatible systems from the biological point of view, capable of providing the sustained release and specific delivery to tissues, organs and cells of drugs, enzymatic systems and genetic material. Cell systems such as bacterial ghosts, erythrocyte ghosts, polymorph nuclear leukocytes, apoptotic cells, tumor cells, dendritic cells, and more recently, genetically engineered stem cells, are all

examples of how cell systems of very diverse nature can be suitably manipulated and loaded with drugs and other substances, to permit specific drug delivery in vivo with important therapeutic applications. Cell carriers for drug delivery are used in very different applications such as cancer therapy, cardiovascular disease, Parkinson's, AIDS, gene therapy, etc. **Table 1** shows the classification of biological carriers for drug delivery based on the use of cells and cell ghosts. [19]

Table-1: Kinds of cells and cell ghosts used for drug and gene delivery

Cell carrier	**Target**	**Encapsulated substance**
Bacterial ghost	Tissues, macrophages, cells	Drugs, vaccines, genetic material
Erythrocyte ghost	RES, macrophages	Drugs, enzymes, peptides
Engineered stem cells	Tumor cells, T cells,	Genetic material
Polymorphonuclear	macrophages	
leucocytes	Tissues	Drugs
Apoptopic cells		
Tumor cells	Tumor cells	Drugs
Denditric cells	Tumor cells	Drugs
	T cells	Drugs

4.8 Quantum dots:

Nanotechnology can be exploited to improve the utility of fluorescent markers used for diagnostic purposes. Although fluorescent markers are routinely used in basic research and clinical diagnostic applications, there are several inherent disadvantages with current techniques, including the requirement of color-matched lasers, the fluorescence bleaching, and the lack of discriminatory capacity of multiple dyes. Fluorescent nanocrystals potentially overcome these issues. Nanocrystals [also called quantum dots (QDs; Qdots) or nanodots] are crystalline clumps

of a few hundred atoms, coated with an insulating outer shell of a different material. Qdots are generally composed of cadmium selenide (CdSe), but now a days it composed many other semi conducting materials derived from the II and VI elemental groups (e.g. CdTe, CdS, CdHg, ZnS) and III and V elemental groups (e.g. InAs, InP, GaAs) of the periodic table. Possessing a size range of 1–10 nm diameters, quantum dots (QDs) are so-called quasi zero-dimensional, single, mostly spherical semiconductor nanocrystals. [20]

4.9 Magnetic nanoparticles:

Magnetic nanoparticles are a powerful and versatile diagnostic and drug carrier tool in biology and medicine. It is well known in chemotherapy is an effective treatment to fight cancer cells, but since it is delivered as a full body dose, the side effects of its toxicity are often severe and devastating to the patient. One proposed use of magnetic nanoparticles that is particularly exciting is for targeted drug delivery. In this application, the magnetic particle is coated with activated carbon and serves to deliver pharmaceuticals to specific sites. In practice, the administered drug is absorbed to the particle and is localized to a specific site in the body by an external magnet field. The physical force created by the external magnetic field acts to transport the particles through the vascular wall, thus positioning and retaining the drugs in close proximity to the cancer cells. This allows for more concentrated doses of the anti-cancer drugs to be delivered to the cancer and keep them on site for longer periods of time. This targeted drug therapy was in phase I and II trials as of June 2000. [21]

Magnetic nanoparticles also used as diagnostic applications. Bound to a suitable antibody, magnetic nanoparticles are used to label specific molecules, cell populations, structures or microorganisms. Magnetic immunoassay techniques have been developed in which the magnetic field generated by the magnetically labeled targets is detected directly with a sensitive magnetometer. Binding of antibody to target molecules or disease-causing organism is the basis of several tests.

4.10 Carbon nanotubes:

Nanotubes are a particularly novel form of nanoparticle about which there is great interest and excitement. Carbon nanotubes (CNT) were first discovered by Iijima (1991), and are a new form of carbon molecule. They are similar in structure to the spherical molecule C_{60} (buckminsterfullerene or bucky balls) discovered in the 1980s (Kroto et al; 1985) but are elongated to form tubular structures 1-2 nm in diameter. They can be produced with very large aspect ratios and can be more than 1 mm in length. In their simplest form, nanotubes comprise a single layer of carbon atoms (single molecule) arranged in a cylinder. These are known as single-wall carbon nanotubes (SWCNTs). They can also be formed as multiple concentric tubes (multi-wall carbon nanotubes, MWNTs) having diameters significantly greater, up to 20 nm, and length greater than 1 mm. [22] Based on their dimensions, their novel electronic structures, and their

controllable chemical functionality, carbon nanotubes and other carbon nanomaterials are expected to be used in several applications, including medical and biomedical areas, such as drug delivery and diagnostic devices. [23]

5. Conclusion:

Nanotechnology is an emerging enabling technology for the 21st century and in recent year's Nanocarrier has emerged as one of the most prominent application fields of nanotechnology. Nanoparticulate-based drug delivery is by far the most advanced field of nanomedicine. The flexibility to modify or adapt nanotechnology to meet the needs of pathologic conditions either for therapeutic applications or as a diagnostic tool is the important characteristic of the technology. Based on the review of the available literature, it could be inferred that although numerous drug delivery approaches are available none of them seems perfect and suffers from one limitation or another. The deep interest and vast invest in nanotechnology enables the researchers to looking forward to new specific drug delivery technology and utilizing these in future development of drug delivery system. The future holds lot of promises in nanoparticulate delivery system and by further study this will be developed as efficient approach for novel, controlled and targeted drug delivery systems.

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