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Nanocarriers for drug delivery applications

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Abstract
Nanotechnology by manipulation of characteristics of materials such as polymers and preparation of nanocarriers is able to provide superior drug delivery systems for better management and treatment of diseases. The nanocarriers employed as drug delivery systems have multiple advantages which make them superior to conventional delivery systems. In this review, we focus on the different types of nanocarriers, their methods of preparation and characterization which are used for drug delivery.

Keywords: drug delivery, nanotechnology, nanocarriers, SEM, TEM

1. Introduction
A major obstacle for most drug delivery systems include poor bioavailability, in- vivo stability, solubility, intestinal absorption, sustained and targeted delivery to the site of action, therapeutic effectiveness, side effects, and blood-plasma concentration of drugs which either fall below the minimum effective concentrations or exceed the safe therapeutic concentrations. However, nanotechnology in drug delivery is an approach designed to overcome these challenges due to the development and fabrication of nanostructures at submicron scale and nanoscale which are mainly polymeric and have multiple advantages (Ochekpe1 *et al*., 2009) [42].

1.1 Nanotechnology
Nanotechnology is derived from the Latin word "nano", which means dwarf. It is used in the production of materials at submicron or molecular level in engineering, electronics, physics and material science. Nanosized materials may be a device, a system of supra molecular chemistry, complexes or compounds. In 1959, the term of nanotechnology was first used by the physicist Richard Feynman (Feynman, 1959) [18]. He indicated that by producing materials and devices at the molecular level, nanostructures can be measured and nanotechnology can be used for many new purposes. The major application areas of nanotechnology are materials and manufacturing sector, nano electronics and computer technology (fibre optic communications networks), aviation and space research, environment and energy, agriculture, chemical engineering, defense industry, biology, biotechnology, medicine and pharmaceutics (Zhang *et al*., 2009) [57].
Nanotechnology is a multidisciplinary field, convergence of basic sciences and applied disciplines like biophysics, molecular biology, and bio engineering. Size reduction is a fundamental unit operation having important application in pharmacy. Major advantages of nano sizing include

- Increase surface
- Enhance solubility
- Increase rate of dissolution
- Rapid onset of action
- The Less amount of the dose required in the field of pharmacy

For applications to medicine and physiology these materials and devices can be designed to interact with a high degree of functional specificity, thus allowing a degree of interaction 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, material science and biology to bring together the required collective expertise needed to develop these novel technologies.
In medicine and pharmaceutics, nanotechnology is used to improve human health at a molecular level. The novel and potential applications of nanotechnology in pharmaceutics are development of diagnostic tools, formulation of drug carrier systems and gene therapy. The advantages of nanotech drugs compared to conventional counter parts lie on the basis of particle size. Drugs/drug products with nano dimension can be used at a lower concentration and can lead to early onset of bioactivity (Chan *et al*., 2006) [11].

2. Nanocarriers
Nanocarriers are colloidal particulate systems. They have been successfully utilized in the diagnosis, treatment and monitoring of various diseases (Oberdorster *et al*. 2005) [41]. Successful development of a drug formulation for any disease requires consideration of the five parameters. This is also known as 5D-approach and comprises of disease, drug, destination, delivery system and dollar or cost of medication. These parameters are interlinked, i.e. selection of drug as well as destination depends on the disease under investigation and similarly, selection of a delivery system depends on physicochemical properties of drugs, the destination or the target area of disease (Panchagnula, 2004) [43].

2.1 Types of Nanocarriers

2.1.1 Polymer-Based Nanoparticles

Polymeric nanoparticles are nano sized particles made of natural or synthetic polymers. These polymers may be biodegradable or non biodegradable. Nowadays, the use of polymeric nanoparticles is one of the most promising approaches for drug delivery (Kreuter, 2007) [30] (Pardridge, 2007) [44]. Depending on the method of preparation, the drug is either physically entrapped or covalently bound to the polymer matrix. The resulting compound has the structure of capsules (polymeric nanoparticles), amphiphilic core/shell (polymeric micelles) or hyper branched macromolecules (dendrimers). The drug is dissolved entrapped, encapsulated or attached to matrix depending upon the method of preparation of nanoparticles, nanocapsules or nanospheres can be obtained (Fig. 1).

Nanosphere Nanosphere is a matrix system in which the drug is physically, chemically and uniformly dispersed (Lee, 2005) [32].

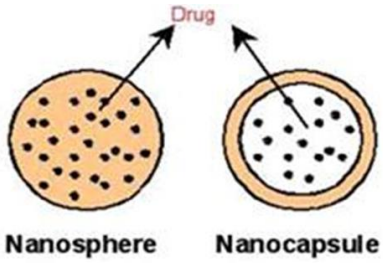


Fig 1: Structure of nanosphere and nanocapsule

Nanocapsule - Nanocapsule is a system in which the drug confined to a cavity surrounded by a unique polymer membrane.

The different aspects of nanoparticles as well as biomaterials employed for their production have been comprehensively reviewed by several research groups. The most widely investigated polymers include; Natural:

Chitosan (Feng *et al*. 2013) [17], Alginate (Ahmad *et al*., 2006) [1], Gelatin (Sundar *et al*., 2010) [53], and Albumin (Elzoghby *et al*., 2012) [16] and Synthetic: Poly (lactic acid) (PLA) (Bourges *et al*., 2003) [8], Poly (lactic co glycolic acid) (PLGA) (Sharma et.al., 2015) [48], Poly (cynoacrylate) (PCA) (Soppimath, 2001) [51], Poly (methacrylic acid ethyl acrylate) (Delie *et al*. 2005) [8], Poly (ethylene glycol) (PEG) (Zweers *et al*., 2006) [58] (Nema *et al*. 2010) [39, 40], Polycaprolactone-b-PEG (Shin *et al*., 1998) [49].

2.1.1.1 Polymeric micelles

Amphiphilic block copolymers assemble into nanoscopic supra molecular core shell structure known as polymeric micelles (Fig. 2). There are usually less than 100 nm and their hydrophilic surface protect their nonspecific uptake by reticulo endothelial system. Micelles formed in the solution as aggregates in which the component molecules are arranged in a spherical structure with the hydrophobic core shield from water by a mantle of hydrophilic group. These are used for systemic delivery of water insoluble, poorly soluble and sparingly soluble drugs and drugs are trapped physically within the hydrophobic cores can be linked covalently to component molecules of the micelles. These have a high loading capacity, stability in the physiological conditions, slower rate of dissolution, high accumulation of drug at the target site and the possibility of functionalization of end group for conjugation of targeting ligands (Maincent *et al*., 1992) [33].

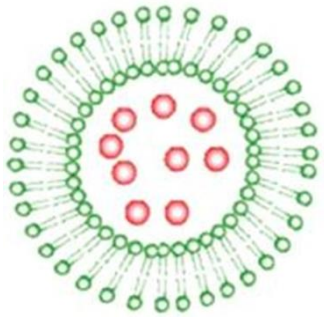


Fig 2: Structure of Micelles

Polymeric micelles are composed of internal and external zones named core and shell, respectively. These materials are also safer for parenteral administration (Strickley, 2004) [52] and display cores and hence, result in higher solubilisation capacity. The hydrophobic character of the core enables the inclusion of hydrophobic drugs by physical means or chemical conjugation and their dispersion at the molecular level, resulting in enhanced water-solubility (Rapoport, 2007) [46] (Jain *et al*., 2009) [26].

Multifunctional polymeric micelles containing targeting ligands and imaging and therapeutic agents are being actively developed and will become the mainstream among several models of the micellar formulation in the near future (Nasongkla *et al*. 2006) [38] (Nema et.al. 2010) [39, 40].

2.1.1.2 Dendrimers

A dendrimer (Fig. 3) is a synthetic polymeric macro molecule of nanometer dimensions, composed of multiple highly branched monomers that emerge radially from the central core. Properties associated with these dendrimers such as their monodisperse size, modifiable surface functionality, multivalency, water solubility, and available internal cavity make them attractive for drug delivery (Svenson *et al*., 2005) [54].

It contains three different regions i. e. core, branches and endings. The core forms the central part and branches radiate from it forming an internal cavity and a sphere of the group (Gupta *et al*., 2015) [22].

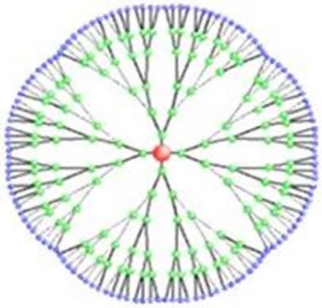


Fig 3: Structure of Dendrimers

2.1.2 Lipid based drug carriers

2.1.2.1 Liposomes

Liposomes (Fig. 4) are self-assembling closed colloidal structures composed of one or more lipid bi-layers which surround a central aqueous space or core. These are three types based on the size and number of bi-layer.

- **Multilamellar vesicles:** These are consisted of several lipid bi-layers separated from one another by aqueous space. These are heterogeneous in size ranging from few hundreds to thousands of nm in diameter.
- **Small unilamellar vesicles and large unilamellar vesicles**

These are consisted of a single bi-layer surrounding the entrapped aqueous space. Small unilamellar vesicles are less than 100 nm and large unilamellar vesicles are more than 100 nm. Drug either entrapped in the aqueous space or intercalated into lipid bi-layers of liposomes (Jain, 2005) [25].

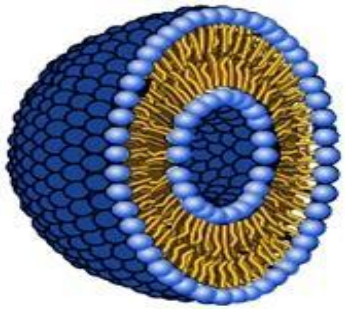


Fig 4: Structure of Liposome

2.1.2.2 Solid lipid nanoparticles (SLNs)

Solid lipid nanoparticles (Fig. 5) have been developed as an alternative delivery system for conventional systems. SLNs are sub-micron colloidal particles which are composed of lipid, dispersed in water or in an aqueous surfactant solution (Muller *et al*., 2000).

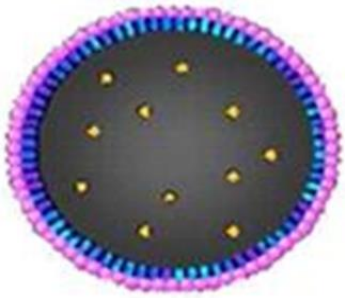


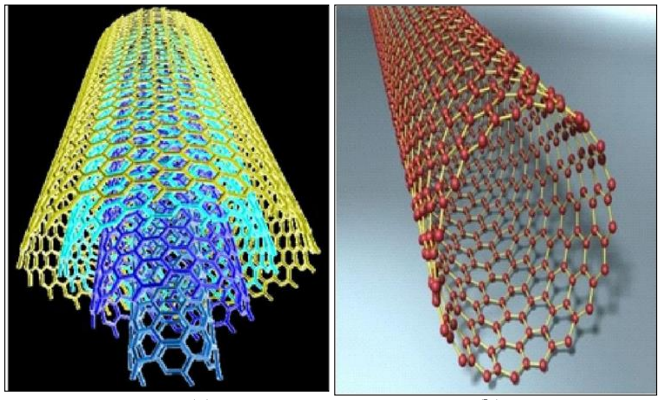
Fig 5: Structure of Solid lipid nanoparticle

SLNs combine advantages of polymeric nanoparticles, fat emulsions and liposomes, but avoid some of their disadvantages. They are biodegradable, biocompatible and non-toxic. Avoidance of coalescence leads to enhanced physical stability. Reduced mobility of incorporated drug molecules leads to reduction of drug leakage. solid/liquid facilitates static interface, surface modification.

2.1.3 Carbon nanotubes

These are hexagonal networks of carbon atoms. The length and diameters of these tubes can be 1 nm to 100 nm in length. Nanotubes are two type's single walled nanotubes and multiwalled nanotubes (Fig 6a and 6b). These are small macro molecules have unique size, shape and remarkable physical properties (Sinha *et al*. 2005) [50].

Carbon nanotubes have been applied in biology as a sensor for detecting DNA and protein, diagnostic devices for the discrimination of different proteins from serum and as a carrier to deliver vaccine or protein. Chemical modifications of carbon nanotubes can render them water solubility and functionalization so that they can be linked to a wide variety of active molecules such as peptides, proteins nucleic acids and therapeutic agents (Bianco *et al*., 2005) [6]. The multiple covalent functionalization on the side wall or tips of carbon nanotubes allows them to carry several molecules at a time, and this strategy provides a fundamental advantage in the treatment of cancer (Pastorin *et al*., 2006) [45].



(a) (b)

Fig 6: (a) Structure of multiwalled carbon nanotube.
(b) Structure of single walled carbon nanotube

3. Methods of Preparation of Nanocarriers

The method used for the preparation of nanocarriers depends on the type and the desired properties of the nanocarriers to be produced. Methods of preparing of polymeric nanoparticles have been reviewed (Mohanraj *et al*., 2006) [36] and they include ionic gelation, coacervation, phase separation solvent evaporation, spontaneous emulsification/ solvent diffusion, salting out/emulsification-diffusion, supercritical fluid technology and polymerization.

Depending on the materials utilized, such as phospholipids and glycolipids, the desired liposome structure can be prepared by sonication, electroformation, extrusion from diluted lamellar dispersions, high-shear homogenization, reverse-phase evaporation, gel exclusion chromatography, freeze lyophilization, calcium-induced fusion, detergent dialysis and ultracentrifugation (Šegota *et al*., 2006) [47] (Huang, 2008) [23].

Syntheses of dendrimers include the use of Tomalia's divergent growth approach, convergent growth approach, and orthogonal coupling strategy (Gilles *et al*. 2005) [21] while solid lipid nanoparticles are prepared by high shear homogenization, ultrasound dispersion technique, high pressure homogeniza-tion, solvent emulsification/evaporation, microemulsion and solvent diffusion (Huo *et al*., 2007) [24].

Methods of preparing polymeric micelles include dialysis,

solution-casting, direct dissolution (Gaucher *et al*. 2005) [20]. Carbon nanomaterials are prepared by template synthesis, the carbon-arc discharge technique, catalytic chemical vapour deposition and laser ablation (Foldvari *et al*., 2008) [19] (Sinha *et al*. 2005) [50].

4. Characterization of Nanocarriers

Nanocarriers are generally characterized by their size, morphology and surface charge, using different techniques.

4.1 Size of nanocarriers

There are several tools for determining the size of nanocarries as discussed below.

4.1.1 Dynamic Light Scattering

Currently, the fastest and most popular method of determining particle size is photon-correlation spectroscopy (PCS) or dynamic light scattering (DLS). DLS is also used to determine the size of Brownian nanoparticles in colloidal suspensions in the nano and submicron ranges (Bera *et al*. 2010) [4]. Laser monochromatic light onto a solution of spherical particles in Brownian motion causes a Doppler shift when the light hits the moving particle, changing the wavelength of the incoming light. This change is related to the size of the particle. It is possible to predict the size distribution and give a description of the particle's motion in the medium by measuring the diffusion coefficient of the particle and using the autocorrelation function (Mattoussi *et al*., 2012) [35].

4.2 Morphology of nanocarriers

The size and morphology of nanocarriers exert a profound influence on the physical and chemical properties that determine their interaction with the environment and biological systems. There are certain techniques to analyze the morphology of nanoparticles. Microscopic techniques like SEM, TEM and AFM, along with particle size also determine other parameters like morphology or surface roughness of the nanoparticles.

4.2.1 Scanning Electron Microscope

For SEM characterization, nanoparticles dispersion should be first converted into a dry powder, which is then mounted on a sample holder followed by coating with a conductive metal, such as gold, using a sputter coater. The sample is then scanned with a focused fine beam of electrons. The surface characteristics of the sample are obtained from the secondary electrons emitted from the sample surface. The nanoparticles must be able to withstand vacuum, and the electron beam can damage the polymer.

4.2.2 Transmission Electron Microscope

TEM operates on different principles than SEM, yet it often brings the same type of data. The nanoparticles dispersion is deposited onto support grids or films. To make nanoparticles withstand the instrument vacuum and facilitate handling, they are fixed using either a negative staining material, such as phosphotungstic acid or derivatives, uranyl acetate, etc., or by plastic embedding. Alternative method is to expose the sample to liquid nitrogen temperatures after embedding in vitreous ice (Amzallag *et al*., 2006) [3]. The surface characteristics of the sample are obtained when a beam of electrons is transmitted through an ultra thin sample, interacting with the sample as it passes through.

4.2.3 Atomic Force Microscopy

AFM is yet another tool used to characterize variety of surfaces, including nanoparticles, at the atomic level and it is one of the primary forms of scanning probe microscopes (Blanchard, 1996) [7]. The prime advantage of AFM is its ability to image non-conducting samples without any specific treatment, thus allowing imaging of delicate biological and polymeric nano and microstructures. AFM requires minimal sample preparation and can be performed in ambient conditions (Magonov, 1993) [4]. Scanning with a sharp probe across its surface and then monitoring and compiling the tip-sample interactions provide the images of the sample surface.

4.3 Stability of nanocarriers

The colloidal stability is analyzed through zeta potential of nanocarriers. This potential is an indirect measure of the surface charge. It corresponds to the potential difference between the outer Helmholtz plane and the surface of shear. Laser Doppler anemometry is the technique used to measure the zeta potential. It is based on the evaluation of the velocity of particles by the shift caused in the interference fringe, which is produced by the intersection of two laser beams. The electrophoresis mobility is then transformed into zeta potential. Most colloidal particles have negative zeta potential values ranging from about −100 to −5 mV.

Surface charges prevent the agglomeration of nanoparticles polymer dispersions because of strong electrostatic repulsion, thereby enhancing the stability of the nanoparticles. The zeta potential can also provide information regarding the nature of material encapsulated within the nanocapsule or coated onto the surface (Pastorin *et al*. 2006) [45].

4.4 Particle Structure

Analysis of structural changes of the free protein sample and protein nanoparticles is imperative to understand the nature of modifications taking place in the protein in terms of confirmation, folding, chemical bonding, etc., during the synthesis of nanoparticles.

4.4.1 X-ray Diffraction

One of the techniques for this purpose is X-ray diffraction (XRD) which is the primary tool for investigating the structure of crystalline materials, from atomic arrangement to crystallite size and imperfections. XRD also analyzes the phase composition, crystallite size and shape, lattice distortions and faulting, composition variations, orientation and *in situ* structure development of the nanoparticles. Usually, the XRD pattern is obtained by illuminating the sample with an x-ray source (Copper K_α line) with wavelength of 1.54Å and scanning the diffraction within a certain range of the angle 2θ.

4.4.2 Fourier Transform Infrared Spectroscopy

Another technique to supplement XRD is Fourier transform infrared spectroscopy (FTIR). The advantage of FTIR over crystallographic techniques is its capability to provide information about the structural details with greater spatial

and temporal resolution (Berthomieu *et al*., 2009) [5]. The sample used for characterization is usually lyophilized nanoparticles in minute quantities. The basic principle that governs is that the bonds and groups of bonds vibrate at characteristic frequencies. A molecule that is exposed to infrared rays absorbs infrared energy at frequencies which are characteristic of that molecule. FTIR analysis is carried out by illuminating the sample with a modulated IR beam. The sample transmittance and reflectance of the infrared rays at different frequencies is translated into an IR absorption plot, which is then analyzed and matched with known signatures of identified materials in the FTIR library.

5. Applications

The use of nano-delivery systems has been extensively reviewed previously. Application of smart nanomaterials such as site-targeted nanomaterials, site-triggered nanomaterials and combined smart technologies for cancer drug delivery (Brewer *et al*., 2011) [9]. Nanotechnology offers opportunities to develop new treatment approaches that could contribute to the cure various type of diseases such as cancer, HIV/AIDS, tuberculosis, and neurological disorder etc.

Table 1: List of nanocarriers used for drug delivery

Type of Carriers	Materials	Drug	Application	Reference
Polymeric Nanoparticles	PLGA	Dexamethasone	Anti inflammatory	Kim et al., 2006
	PLGA	Rifampicin	Anti tuberculosis	Tripathi et al., 2010
	PBCA	Dalargin	Treatment of neurological disorder	Alyautdin et al., 1995
	Ethyl Cellulose	Repaglinide	Antidiabetic	Dhana Lekshmi et al., 2012
	Eudragit®/PLGA	Diclofenac sodium	Anti inflammatory and analgesic	Cetin et al., 2010
Solid lipid nanoparticle	Soya phosphatidyl-choline 95%	Doxorubicin	Anti Cancer	Zara et al., 2002
Liposome	Phospholipids and cholesterol	Cisplatin	Anti Cancer	Kakinuma et al., 1996
Dendrimer	Mannosylated poly(propyl eneimine)	Lamivudine	Anti HIV	Dutta et al., 2007
	Polyamidoamine (PAMAM)	Ibuprofen	Anti-inflammatory	Kolhe et al., 2003
Polymeric Micelle	α-methyl-ω-aminopoly(oxyethylene)	Isoniazid	Anti tuberculosis	Eiizabeth et al., 2007
Carbon nanotubes	Phospholipid-branched polyethylene glycol.	Paclitaxel	Anti Cancer	Liu et al., 2008

6. Conclusion

The use of Nanotechnology in medicine and more specifically drug delivery is set to spread rapidly. Nanostructured delivery architectures are promising candidates that will enable efficient and targeted delivery of novel drug compounds. Sustained drug release and intracellular entry capability are properties of nanoscale drug delivery mechanisms that will minimize side effects and allow for the direct treatment of the cause of the disease rather than the symptoms of the disease. It is anticipated that better understanding and application of nanotechnology for effective drug delivery would ultimately enhance efficacy of treatment and patient drug use compliance.

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