NATURE OF NANOPARTICLES AND THEIR APPLICATIONS IN TARGETED DRUG DELIVERY

H. Zulfiqar[1], S. Hussain[1*], M. Riaz[2], A. Saddiqa[3], M. Iqbal[4], J. Ali[1], M. Amjad[1] and K. Javaid[1]

[1]Department of Chemistry, Lahore Garrison University, Lahore, Pakistan
[2]Department of Chemistry, University of Sargodha, Pakistan
[3]Department of Chemistry, Government College University, Lahore, Pakistan
[4]Department of Chemistry, Government College University, Faisalabad, Pakistan
*Corresponding Author's E-mail: dr.shabbirhussain@lgu.edu.pk

ABSTRACT: Nanotechnology is a rapidly growing field and has secured a prominent rank in medicinal field. They find applications in cancer therapy, cell bio-imaging, in treatment of neurodegenerative diseases, in targeted drug delivery at cell or tissue level and also in the regeneration of tissues and different organs. NPs like liposomes and dendrimers are widely used as nanocarriers. They can be successfully employed in drug delivery due to their specific properties like bioavailability, their biocompatibility and accumulation only at the specific target site without harming or affecting other non target tissues. They are superior in targeted drug delivery as compared to the conventional methods of drug delivery. Nanoparticles (NPs) are synthesized by various techniques and approaches.

Key words: Nanoparticles; Nature; Drug Delivery; Nanocarriers; Dendrimers.

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INTRODUCTION

Nanotechnology is an emerging and fast growing field of this century. It is imparting a vital role in the world's economy, industry and in people's lives (Abbas *et al*., 2016; Dasgupta *et al*., 2015; Javed *et al*., 2018; Rehman *et al*., 2019; Shahzady *et al*., 2019). The nanotechnology uses knowledge from different fields like physics, chemistry, biology, health sciences and engineering and affecting all the fields of science and human life strongly (Moritz Geszke-Moritz, 2012). Nanotechnology encompasses the characterization, manufacturing and/or manipulation of different structures, devices or materials having at least one dimension that is approximately 1–100 nm in length (Duncan, 2011).

The term "Nanotechnology" was coined first by Prof. Norio Taniguchi in 1974 (Godwin *et al*., 2015). The invention of the Scanning Tunnelling Microscope (STM) in 1982 and the Atomic Force Microscope (AFM) in 1986 was of significant importance in the development of nanotechnology because it was possible to observe structures at the atomic scale with their help. In 1986, Eric Drexler wrote a book entitled "*Engines of Creation*" which introduced the knowledge of nanotechnology to the general public. The discovery of fullerene in 1985 and that of carbon nanotubes in 1991were important steps in the synthesis of nanostructures (Moritz Geszke-Moritz, 2012).

Keeping in view the greater importance of nanotechnology, current studies were performed to overview the nature of nano-particles and their role of nanoparticles in targeted drug delivery.

Nature of nanoparticles: Nanoparticles are those particles with their sizes in the range of 1- 100 nm (Song Kim, 2009). A nanometer is billionth part of a meter, which is 250 millionth of an inch, 10 times of the diameter of hydrogen atom or having diameter about 1/80,000 of the diameter of a human hair (Godwin *et al*., 2015). NPs can be classified into airborne ultrafine particles (UFP) and engineered nanoparticles (ENPs). Particles of dust, soot and smoke that are airborne and present in the atmosphere are called as airborne ultrafine particles and those which are synthesized in laboratories and created artificially are called as ENPs (Wong *et al*., 2017). Nanoparticles differ from the bulk material in their size distribution and morphology; they possess high surface area to volume ratio because reduction in size increases the surface area (Song Kim, 2009). High surface area renders nanoparticles excellent catalytic activity resulting in production of more efficient and energetic materials, small size is responsible for finer polishing and smooth surface of materials (Pitkethy, 2003). NPs are also categorized on the basis of origin, dimensions and structural configuration. Classification on the basis of origin consist of two main groups natural nano-materials and artificial nanomaterials. Natural nanomaterials are those which are present naturally in natural things like viruses, enzymes, proteins and minerals etc. Artificial nanomaterials are those which are not present in nature but are manufactured artificially through some chemical or physical reactions. Dimensionally nanomaterials are categorized into four main classes including zero dimensional nano-materials_arenano-sized crystals (e.g., metallic and semiconductor materials), one dimensional materials

(e.g., nanotubes, nanowires and nanobots), Two dimensional materials (e.g., nanocomposites and nanoplates) and Bulkers (the three dimensionslnanomaterials). On the basis of structural configuration, nanomaterials are classified into four main groups; metallic nanomaterials, carbon based nanomaterials, dendrimers and composites

Chemical classification includes organic and inorganic nanomaterials. Inorganic structuresinclude metal oxide nanoparticles, semimetal oxides, metalnanoparticles, semiconductor, quantum dot or carbon structures (nanotubes, graphene, fullerenes). Organic structuresinclude polymer nanoparticles or dendrimers (Moritz Geszke-Moritz, 2012).

Role of nanoparticles in targeted drug delivery: Implementation of the rules of nanotechnology in the field of medicine comes under the term of nanomedicine (L. Zhang *et al*., 2008). In other words we can also say nanomedicine as the subset of nanotechnology. Nanotechnology is applicable in medicine in cancer therapy, cell bio-imaging, in treatment of neurodegenerative diseases, in targeted drug delivery at cell or tissue level and also in the regeneration of tissues and different organs (Moritz Geszke-Moritz, 2012).

Nanoparticles are used in medicine because of enhancement in their different properties like their solubility, their diffusion capacity, blood circulation, half life, drug release characteristics and immunogenicity (Zhang *et al*., 2008). The nanoparticles which are being used in targeted drug delivery constitute a new class of medicine and have proved to be useful because of their ability to provide increased efficacy and reduced toxicity (Bartlett *et al*., 2007), more convenient route of administration, augmenting the product's life cycle and ultimately reduction in health care cost (Zhang *et al*., 2008). Nanoparticles also enhance the drug solubility and reduce its metabolism by dissolving them either in hydrophilic head or hydrophobic tail. Nano-medicines are also becoming significant because of their increased half life in plasma and different biodistribution as compared to common therapeutics. Nanoparticles also show enhanced permeability and retention effect (ERP); the effect is due to accumulation of nanoparticles in the target area and is responsible of reducing the toxicity effect of the drug on the normal tissues or the cells other than the targeted area (Kumari *et al*., 2016). About 31 years ago the ERP effect was demonstrated by Maeda and coworkers that the nanosized particles exhibit enhanced ERP effect by accumulating in tumors after passing via the leaky neo-vascular walls in the tumors. According to them the nano size is vital in altering the drug's bio-distribution and making it more effective (E. Liu *et al*., 2018). Nanoparticles make the transportation of drugs at the inflammation site quite easy (Kim Dobson, 2009). Also the transmission system of antitumor drugs is aided by degradable polymer nanomaterials (Pandey *et al*., 2004; Wu *et al*., 2018).

What is drug and targeted drug delivery: The small organic molecules or agents used for the degradation of diseased proteins are called as drugs. These diseased protein are formed as a result of some interaction or interferences of pathogens at the cellular level (Pandey *et al*., 2004).

Targeted drug delivery literally means delivery of any drug only to a specific area (called as target area) and not affecting the non target area. This approach is getting immense importance in oncology applications *i.e*., in the formation of more effective therapeutics (Bartlett *et al*., 2007). Drug delivery to the body can be categorized broadly as: (I) Local (II) systemic. The drug delivery outside the body comes under heading of local drug delivery while that involving the internal body structures is called systemic drug targeting. Drug targeting is of three types

- First order targeting that is to a discrete organ or tissue.
- Second order targeting involves targeting to a specific cell type.
- Third order targeting - implies delivery to specific intracellular compartments in the target cells e.g., Lysosome (Sutton *et al*., 2007).

The easiest and most preferred route for drug delivery is the oral drug ingestion. The poor solubility and low permeability of these orally administered drugs results in their low bioavailability. Their bioavailability is made easy by encapsulating them in nanoparticle carriers, possessing exceptional physiochemical properties (G. Liu *et al*., 2019).

Targeted drug delivery using nanoparticles is based on efficient drug encapsulation, successful drug delivery to the target region (tissue/cell) and successful drug release at target area (Fymat, 2017).

Nanoparticles which are applied in drug delivery are of size between (100-1000nm) and may involve particles, devices or special system synthesized from special materials like polymers, lipids, viruses and inorganics. Those made from polymers include polymeric nano-particles, micelles, vesicles or dendrimers. Liposomes are those which are made from lipids, viral nanoparticles are prepared from viruses, etc. (Xin *et al*., 2017). Figure-1 shows some important nanomaterials. Metal nano-particles of Ag, Au, Ce, Cu, Eu, Fe, Se, Ti, Y, carbon and silicon etc have been used as prominent therapeutic agents and drug delivery carriers (Li *et al*., 2018). Similarly hydrogels and polymersomes are also important delivery vehicles (Zhang *et al*., 2018). The nanotechnology involves treatment of cancer, asthama, hypertention, diabetics and neurodegenerative diseases through the drug delivery system (Wanigasekara Witharana, 2016).

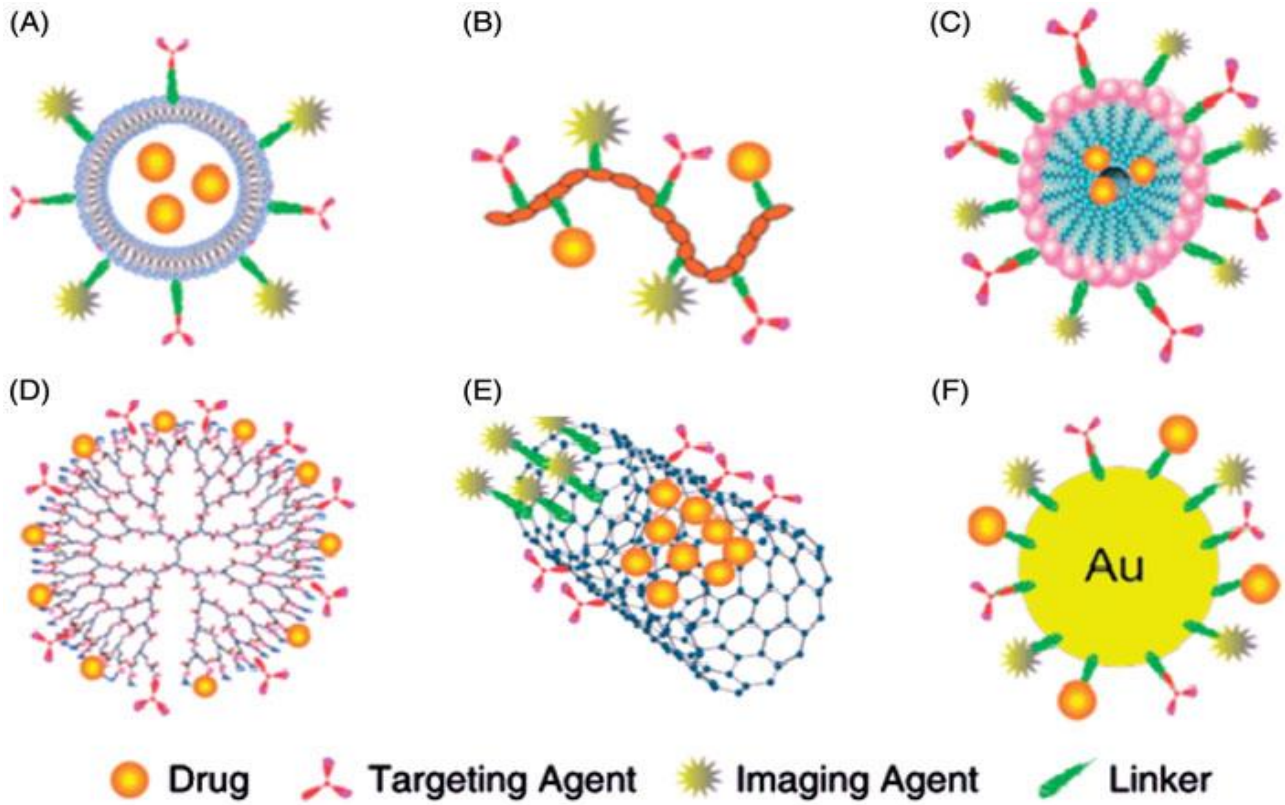

Figure-1: Different nanomaterials (a) liposomes, (b) polymer conjugate, (c) micelles, (d) dendrimers, (e) carbon nanoparticles and (f) inorganic (metal) nanoparticles (Kumari *et al*., 2016)

How nps perform the targeted drug delivery action: Materialsor substances which carry drugs encapsulated within them are called as carriers. Carriers are basically of two types; synthetic carriers and natural carriers. The synthetic carriers which are used in drug delivery include polylactic acid (PLA), Poly (DL-lactide-co-glycolide) (PLG), polyglycolic acid (PGA), polyanhydrides, polymethyl acrylates, etc. whereas natural carriers of drugs includelipids (liposomes and solid lipid nanoparticles), alginic acid, chitosan, gelatin, dextrins etc. Nanocarriers help in different delivery system designing and provide selectivity in choosing delivery route (Fonseca-Santos *et al*., 2015). The drug or therapeutic agent are either adsorbed or covalently attached or encapsulated into these nanocarriers and the surface of these NPs can be made functional by attaching either synthetic polymers or appropriate ligands to the surface. By using such techniques the drug delivery system can be made controllable (Cho *et al*., 2008).

The nanomaterials which carry drug during delivery are called as nanocarriers. The delivery characteristics of these drugs become totally different due to the encapsulation in these nanocarriers which results in the shielding effect of these nanodrug delivery systems (nano-DDS) (Figure-2). The drugs are encapsulated within these carriers through various interactions between the carrier and the medicine mainly long range electrostatic interaction. Other factors which causes release of drug at the target site includes different pH values, temperature ranges and external applied magnetic fields *etc*. Two of the most popular routes which have utilized the recent drug delivery system are based upon the pulmonary and nasal routes (Singh *et al*., 2008).

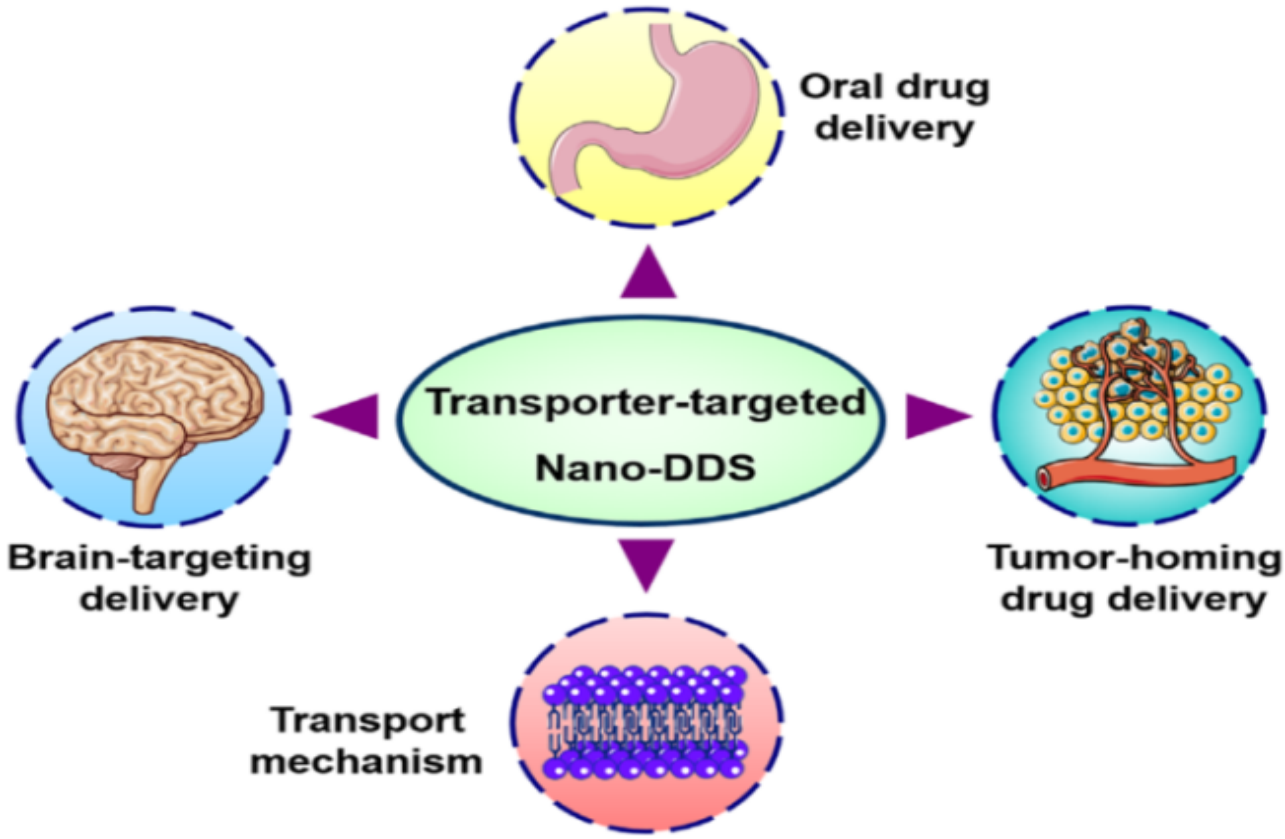

Figure-2: New trends in targeted nano-DDS (Su *et al*., 2018)

Nanoparticles (NP) act as an efficient delivery systems for nasal vaccines and also helpful in improving the delivery of antigens to immune cells (Lê *et al*., 2019).

Liposomes as drug carriers: Liposomes are extensively talked about and highly developed nanocarriers having the size of 20-10000nm. These are small and artificially synthesized vesicles consisting of lipid bilayers (Figure-3) (Paliwal, 2014). Liposomes possess both liposomes hydrophobic and hydrophilic components in their structure. The hydrophilic end can solublise or carry the water soluble medicine and the phospholipid layer carries fat soluble drugs (Singh *et al*., 2008). In this way liposome can carry both hydrophilic and hydrophobic drugs incorporated into their head, tail or core to the targeted area. This nano-vehicle for carrying drug is getting immense importance and is becoming a highly accepted approach in this era. Basically the interaction of these nano-carriers with the tissues is a quite complex phenomenon. This interacting phenomenon includes various parametersi.e. fusion, endocytosis, adsorption on some surface or lipid transfer (Cooper *et al*., 2014). Liposomes are used because they are just similar to living tissues or cells and they do not experience immune rejection, they augment the drug solubility, enhance metabolism, cause reduction in the side effects and increase activity against cancer cells. The physical appearance of liposomes is dependent on the selected and the target site. Due to the low toxic evaluation of liposomes they are used to deliver DNA, RNA, proteins, antisense oligonucleotides, both hydrophobic and hydrophilic chemotherapeutic agents to the target area. The various drugs which can be encapsulated within these liposomes includes anticancer drugs, antibiotic neurotransmitters and anti-inflammatory drugs (Wanigasekara Witharana, 2016).

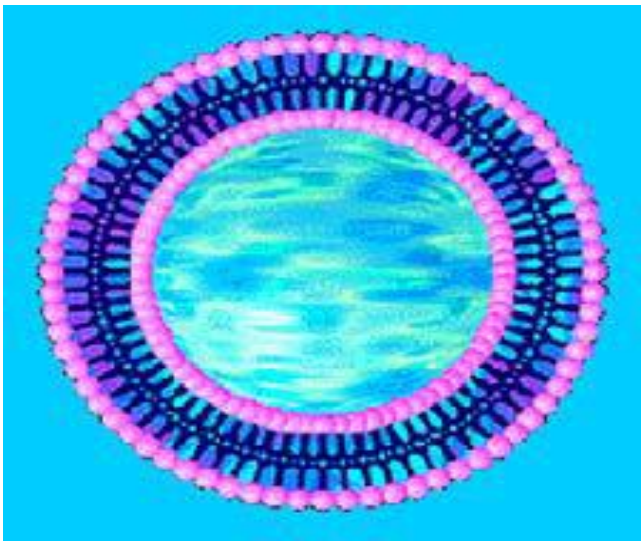

Figure-3: Liposome structure (Chaturvedi *et al*., 2018)

Dendrimers

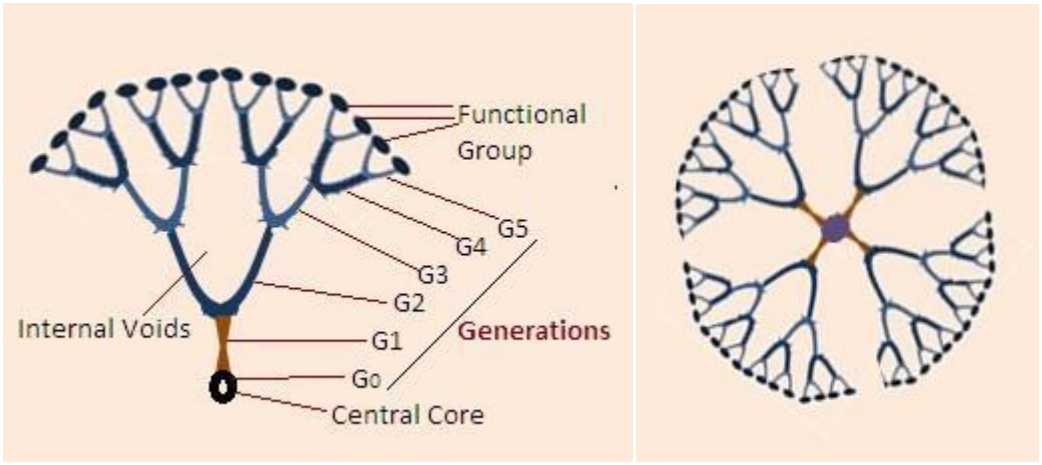

Figure-4: Schematic representation of dendrimer structure (Nikalje, 2015).

Dendrimers (Figure-4) are intensively branched, packed surface tree like structures having three main regions present within them, the core, the branching unit and the surface. A dendrimer has pores in its globular structure (Nikalje, 2015). These act as nanocarriers because they carry drugs. They are manufactured by two main methods 1-divergent method 2- convergent method.

The divergent method includes growth of dendrimers outward from central core and the convergent method includes growth towards the central core. The dendrimers vary in the structure and properties which depends on hydrogen bonding capability, charge and size etc. dendrimers attached to the drugs by covalent bonding and drug attached to its peripheral group. The release of drug into the specific area is governed by nature of the bonding (Chaturvedi *et al*., 2018). Dendrimers act as naocarriers because they can easily cross cell barriers. These are becoming attractive due to high drug loading capability. The various drugs can be attached in the interior or exterior of dendrimers because they posses various functional groups attached to them. They carry drugs either by encapsulation or by interaction with surface groups. Generally two methods of drug delivery include non-covalent encapsulation of drugs and covalent drug-dendrimer conjugates. Dendrimers are involved in a variety of drug delivery systems including CNS delivery, intravenous delivery, gene delivery, cellular deliverer, solubility enhancer, targeted delivery, pulmonary delivery, transdermal delivery, ocular delivery, vaccines delivery, nasal delivery, oral delivery etc (Parajapati *et al*., 2016).

Conclusion: Nanoparticles are superior in targeted drug delivery as compared to the conventional methods and find applications in cancer therapy, cell bio-imaging, in treatment of neurodegenerative diseases and in the regeneration of tissues/organs. They carry the drugs and

successfully deliver them to the specific areas of body, with only little toxic/side effects. Liposomes and dendrimers are widely used nanocarriers in this regard.

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