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Nanotechnology in drug delivery applications: A review

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Abstract

Recent innovation in nanotechnology has shown wonderful promise to revolutionize drug delivery applications by generating novel 'nano-deliveries' that might allow more efficient targeted delivery of various drug molecules, which will reduce or limit systemic side-effects and allow for more efficient use of the drug. But prior to application of them, considerable challenges related to clinical toxicities should be taken into consideration. This review will focus on the various new drug delivery approaches in the context of advances in nanotechnology.

Key words: Nanotechnology; Nanoparticle; Dendrimers; Solid lipid nanoparticles; Drug delivery; Toxicity.

INTRODUCTION

Nanotechnology, a multidisciplinary scientific undertaking, involves creation and utilization of materials, devices or systems on the nanometer scale. The new and unique applications offered by nanotechnology in diverse areas have made it so popular that it is being applied today in almost all aspects of daily life. Nanotechnology has achieved the status as one of the vital research endeavors of the 21st century, which may be called a 'nano-century' with nanotechnology making its presence felt in different spheres of lives. It is generating a diverse array of products with application in several fields including drug delivery, diagnosis, imaging etc [1-2].

Nanoparticles are defined as particulate dispersions or solid particles with a size in the range of 10-1000 nm. Nanoparticles are substantially smaller than eukaryotic or prokaryotic cells; their size is comparable to that of an antibody or virus.[3-4] Nanoparticles can enter into smallest capillary vessels due to their ultra-tiny volume size and avoid rapid clearance by phagocytes, so that, their duration in the blood stream is greatly prolonged. They can penetrate cell and tissue gaps to arrive at the target organs like lung, liver, spleen, bone, brain, spinal cord and lymph.

During last few decades, there has been a considerable research interest in the area of nanoparticle-based drug delivery systems as carriers for various small and large molecules. The drug is dissolved, entrapped, encapsulated or attached to nanoparticle matrices. Nanoparticle-based drug delivery systems have been used as a physical approach to alter and improve the pharmacokinetic and pharmacodynamic properties of various types of drug molecules. They are able to show controlled release properties due to their biodegradability, pH, ion and temperature sensibility.[5] Presently, nanoparticles have been widely used to deliver antibiotics, anticancer agents, radiological agents, vaccines, proteins, polypeptides, antibodies, genes and so on. The major goals in designing nanoparticles as delivery systems are to control particle size, surface properties and release of pharmacologically active agents in order to achieve the site-specific action at the therapeutically optimal rate and dose regimen. Nanoparticle-based drug delivery systems may offer plenty of advantages over conventional dosage forms, which include improved efficacy, reduced toxicity enhanced biodistribution and improved patient compliance.[6] In spite of these advantages, nanoparticles exhibit few limitations also.[7] For example, their small size and large surface area can lead to particle-particle aggregation, making physical handling of nanoparticle difficult in both liquid and dry forms. In addition, these readily results limited drug loading and initial burst release of drugs. These practical problems have to be overcome before nanoparticle can be used clinically in the development of drug delivery applications. The present paper intends to overview various nanotechnology approaches that found applications in drug delivery.

1. Various nanotechnology approaches for drug delivery applications

Nanotechnology has received a lot of attention with the never-seen-before enthusiasm, because of its future potential that can literally revolutionize each field in which it is being exploited. In drug delivery, nanotechnology is just beginning to make an impact. Many of the current 'nano-delivery' systems, however, are remnants of conventional drug delivery systems that happen to be in the nanometer range, such as dendrimers, solid-lipid nanoparticles, polymeric nanoparticles, polymeric micelles, liposomes, nanosuspensions and nanocrystals, ceramic nanoparticles, carbon nanotubes (CNTs), quantum dots (QDs), gold nanoparticles, polymersomes etc.

1.1. Dendrimers:

Dendrimers are perfect monodisperse macromolecules with regular and highly branched 3-D architecture. They represent novel class of polymers, which are different from traditional polymer type. Dendrimers consist of a series of chemical shells, namely an interior small core; interior layers (generations) composed of repeating units, radically attached to the interior core and exterior (terminal functionality) attached to the outermost interior generations.[8] Dendrimers used in drug delivery and imaging are usually 10 to 100 nm in diameter with multiple functional groups on their surfaces rendering them an ideal carrier systems for targeted drug delivery. The size of dendrimers can influence the extravasations across the endothelium into the surrounding interstitial tissue to reach the target sites.

Dendrimers can be synthesized by either divergent or convergent approaches. In the former approach, the dendrimers is synthesized from the core as the starting point, and each successive generation will be built. The convergent approach of synthesis capitalizes on the symmetrical nature of the dendrimers, where synthesis begins at the periphery of the final molecule and stops at the core where dendrimers segment couple.

One of the stellar characteristics of dendrimers is that they are able to carry various drug molecules in their interior. Drug molecules can be incorporated into dendrimers via. either complexation or encapsulation (Fig. 1). Examples where dendrimers are used as carriers for non-steroidal anti-inflammatory drugs (NSAIDs), anticancer agents, antimicrobial and antiviral drugs.[9] Dendrimers have also been extensively investigated for gene delivery.[10] Dendrimers seem to have immense potential as the solubility enhancers for poorly soluble drugs like ibuprofen.[11] The solubility enhancement was occurred due to electrostatic interaction of carboxyl group of drug with the amino group of dendrimer.

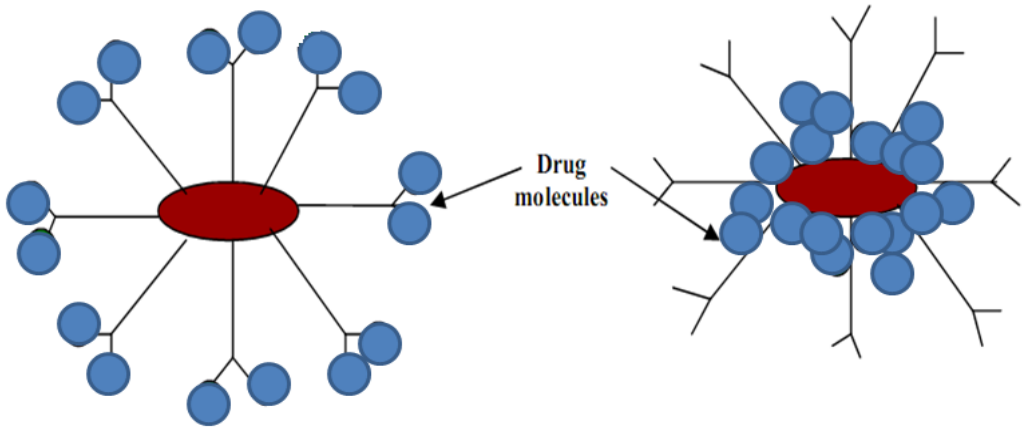

Fig. 1. Schematic of incorporation of drug within a dendrimer structure
Complexation—covalent attachment to end groups (left)
Encapsulation— entrapment inside dendrimer core (right)

1.2. Solid-Lipid Nanoparticles:

Solid-lipid nanoparticles has attracted significant interest by various researchers since the mid 1990s as an innovative carrier system for drug delivery applications because of their physical stability, protection of incorporated labile drugs from degradation, controlled release and excellent tolerability. They are particles of submicron size (50 to 1000 nm) made from lipids that remain in a solid state at room as well as body temperature. Most commonly used solid lipid nanoparticles are spherical objects made of biodegradable materials, such as proteins (i.e., albumin or collagen), fats, or polymers (Fig. 2). Solid lipid nanoparticles can be administered by various routes like oral, parenteral, topical, ocular, pulmonary, duodenal and rectal.[12] Depending on the routes of administration and drugs to be incorporated, solid lipid nanoparticles can be synthesized by different techniques like high-pressure homogenization, microemulsion, w/o/w double emulsion, solvent evaporation, high speed stirring and ultrasonication.

Lipophilic drugs can be better delivered by solid-lipid nanoparticle.[13] Various anticancer agents like doxorubicin, daunorubicin, pacltitaxel, camptothecins, etoposide, flurodo oxyuridine etc have been encapsulated using this particular nanotechnological approach.[14] They have many advantages, such as good biocompatibility, low toxicity and stability. Tobramycin-solid lipid nanoparticles administered duodenally provides good absorption by the gastrointestinal tract (GIT), while tobramycin is still only administered by the parenteral route.[15] The skin has also been targeted in many dermatological and transdermal applications of solid lipid nanoparticles.[16-17] Topical ocular administration of solid lipid nanoparticle dispersions improves the passage of drug molecules into the aqueous humour.[18] Several obstacles frequently encountered with anticancer agents, such as a high incidence of drug resistant tumor cells can be partially overcome by delivering them using solid lipid nanoparticles.[19]

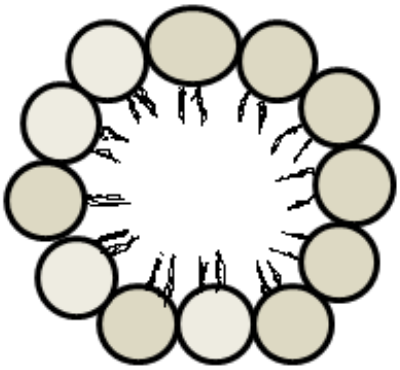

Fig. 2: Structure of solid lipid nanoparticles

1.3. Polymeric nanoparticles:

Polymers play an important role in enhancing the quality of dosage form design and thus improving patient compliance.[20] Polymeric nanoparticles constitute a versatile drug delivery system, which can potentially overcome physiological barriers, and guide the drugs to specific cells or intracellular compartments. They are mostly vesicular or spherical systems in which drug molecules are physically and uniformly dispersed within polymeric matrix systems.[21] Polymeric nanoparticles are made from copolymers to increase circulation half life and inactivation. Various biodegradable polymers like poly lactic acid (PLA), poly lactide glycolic acid (PLGA), and poly ∞-caprolactone are used to prepare polymeric nanoparticles. Methods involved in the preparation can be broadly into two general classes. The first class involves the polymerization of monomers, second is based on the dispersion of preformed polymers. The use of biodegradable polymers for nanoparticle preparation allows controlling the release pattern of drug and sustaining drug levels for a long time by appropriately selecting the polymeric carriers.[22] They usually exhibit a long shelf life and a good stability on storage. A wide range of polymer has been used in the manufacturer of nanoparticles for ophthalmic drug delivery including poly alkyl cyanoacrylate, poly lactic acid and albumin.[23]

1.4. Polymeric micelles:

Polymeric micelles are actually supramolecular, self-assemblies of block copolymers, having a characteristic core-shell structure (Fig. 3). The inner core of polymeric micelles serves as nanocontainer for hydrophobic molecules surrounded by outer shell of hydrophilic flexible tethered strands of polymers.[24] Recently, they have been extensively studied as drug carriers.[25] Drugs can be partitioned in the hydrophobic core of the micelle and the micelle core acts as drug reservoir. The outer hydrophilic layer forms a stable dispersion in aqueous media, which can be administered intravenously. Polymeric micelles have demonstrated high durability in the blood stream and effective tumor accumulation after their systemic administration.[24-25] To support prolonged systemic circulation, polymeric micelles are designed to be biocompatible and thermodynamically stable in physiological environment.[26] The better thermodynamic stability of polymeric micelles indicates low critical micelle concentration (CMC), which prevents *in vitro* rapid dissolution.[24] They are currently recognized as one of the most promising nanocarrier system for drug and gene delivery in the treatment of various diseases. Polymeric micelle-based drug delivery has several benefits over other anticancer drug delivery systems like drug solubility, prolonged half-lives, efficient drug loading without any chemical modification of the parent drug, evading defenses, selective accumulation at the tumor site and lower toxicity. Polymeric micelles can be modified using piloting ligand molecules for targeted delivery to specific target site and pH-sensitive drug-binding linkers can be added for controlled drug delivery.[27]

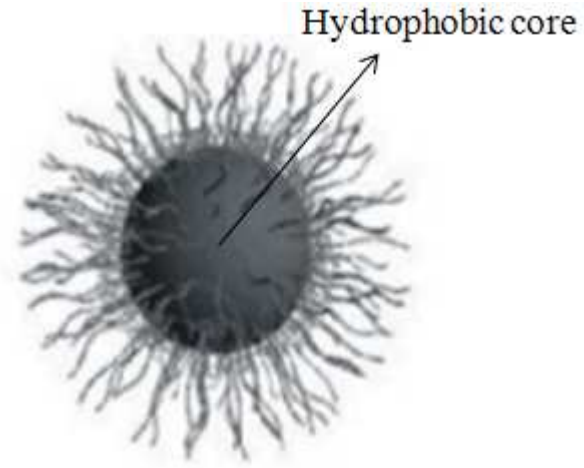

Fig. 3: Polymeric micelles

1.5. Liposomes:

Liposomes have been extensively investigated as a potential drug delivery system due to the enormous diversity of structure and composition that can be achieved. Liposomes are small artificial spherical vesicles composed of non-toxic phospholipids and cholesterol, which self-associate into bilayers to encapsulate drugs, genes and other biomolecules on aqueous interior (Fig. 4).[13,28] The size of liposomes within the range of 25 nm to 10 µm, depending on their preparation method and can be uni- or multi-lamellar. Their properties have been extensively investigated and can vary substantially with desired size, lipid composition, surface charge, and method of preparation.

Various therapeutic agent loaded liposomes are being tested extensively as the targeted delivery for fighting against various diseases.[29-30] Due to their biphasic character, liposomes can act as carriers for both lipophilic and hydrophilic drugs. Depending upon their solubility and partitioning characteristics, the drug molecules are located differently in the liposomal environment and exhibit different drug entrapment and drug release properties. Lipophilic drugs are generally entrapped almost completely in the lipid bilayers of liposomes. Since they are very poorly soluble in water, problems like loss of entrapped drug on storage are minimal with this class of drug. Hydrophilic drugs may be entrapped inside the aqueous core of liposomes. However, it is also possible that hydrophilic drugs are located in the external water phase. The percentage of hydrophilic drug encapsulated by liposomes depends on the liposome bi-layer composition and preparation procedure. Encapsulating insulin in liposomes results in enhanced oral absorption of insulin.[31] Liposomes are currently investigated for a variety of additional therapeutic agents; anticancer drugs such as paclitaxel, camptothecin, cisplatin etc; antibiotics such as amikacin, vancomysin, ciprofloxacin; biologics such as antisense oligonucleotides, DNA.

Liposomal delivery of drug molecules can potentially enhanced transdermal drug permeation.[32] Liposomes may act as permeation enhancers by penetration of individual lipid components. Phospholipids are able to diffuse into the subcutaneous membrane. The interactions and enhancer effects of liposomes on the subcutaneous are based on the lipid mixing of liposomal phospholipids with lipid bilayers of the skin.[33] In some cases, phospholipids themselves can be increased the solubility of lipophilic drugs such as indomethacin and miconazole.[34]

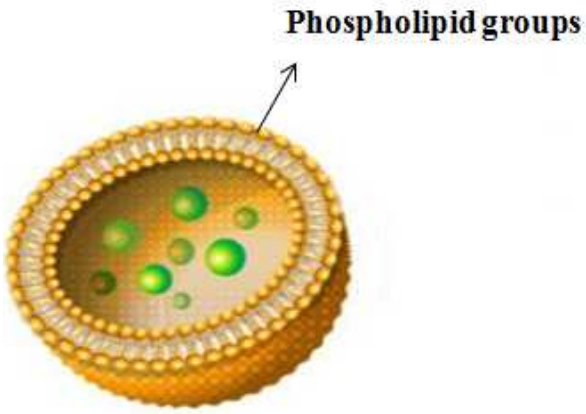

Fig. 4: Liposomes

1.6. Nanocrystals and nanosuspensions:

Poorly soluble drugs are transferred to drug nanocrystals by high pressure homogenization process. This is also possible by milling drug particle using additional milling agents.[35] The drug powders are dispersed in a surfactant solution and the forces in the high pressure homogenizer are strong enough to disintegrate the coarse drug powder into drug nanoparticles. Dispersion media for drug nanocrystals are either aqueous media (e.g., water-ethanol mixtures, isotonic water glycerol mixtures) or non-aqueous media leading to nanosuspensions suitable for parenteral, oral and topical administration.[36]

1.7. Ceramic nanoparticles:

The newly emerging area of using ceramic nanoparticles with entrapped biomolecules has potential biomedical applications including drug delivery.[37-38] Ceramic nanoparticles are made up of ceramic materials such as silica, alumina, titania, calcium phosphate, hydroxyapatite, glass ceramics etc. Their preparations are simple, can be easily prepared with desired size, shape and porosity. The ceramic materials used are biocompatible and their surfaces can be easily modified with different functional groups for ligand attachment. The ultra low size of ceramic nanoparticles (> 50 nm) can help them evade by the reticulo endothelial systems (RES) of the body. In addition, there are no swelling problems and porosity changes with the change in pH. Recently, nanohydroxyapatite ceramics are investigated for various antibiotic delivery applications.[39]

1.8. Carbon nanotubes (CNTs):

Carbon nanotubes consist of exclusively carbon atoms arranged in a series of condensed benzene rings rolled-up into tubular architecture (Fig. 6).[40] They have interesting physical properties such as: ordered structure with high aspect ratio, ultra-light weight, high mechanical strength, high surface area, high electrical and thermal conductivity. The combination of these characteristics make carbon nanotubes a unique carrier with the potential diverse applications, including drug delivery applications.[40-43] A recent study has shown that among a group of different types of nanoparticles, Carbon nanotubes were the delivery systems offering the best improved bioavailability of erythropoietin (EPO).[44]

Fig. 6: Carbon nanotube

1.9. Quantum dots (QDs):

Quantum dots can be prepared from semiconductor materials by electrochemistry or by colloidal synthesis. The common quantum dots are cadmium selenide (CdSe), cadmium telluride (CdTe), indium phosphide (InP), indium arsenide (InAs) etc.[12] Quantum dots can be conjugated to ligands. In a recent study, Bagalkot et al has used QD-aptamer-doxorubicin (Dox) conjugate for targeted cancer therapy.[45] It was shown that the multifunctional QD-aptamer-doxorubicin (Dox) conjugate system can target prostate cancerous cells and sense the Dox delivery by activating fluorescence of quantum dots, which concurrently images the cancerous cells. But unfortunately, under some conditions, quantum dots become cytotoxic.[46] Modification of quantum dots by PEG glycation and micelle encapsulation may limit cytotoxicity.[47] Research on quantum dots is continuing to find biocompatible and effective quantum dots.

1.10. Gold nanoparticles:

Gold nanoparticles have recently emerged as an attractive candidate for delivery of various payloads into their targets.[48-49] The gold core is essentially inert and non-toxic. Gold nanoparticles exploit unique physical and chemical properties for transporting and unloading pharmaceuticals.[48]

Drug delivery systems provide positive attributes to a ‘free’ drug by improving solubility, *in vivo* stability, and biodistribution. They can also alter unfavorable pharmacokinetics of some ‘free’ drugs. Moreover, huge loading of pharmaceuticals on drug delivery systems can render ‘drug reservoirs’ for controlled and sustained release to maintain drug level within therapeutic window. For example, a gold nanoparticle with 2 nm core diameter could be, in principle, conjugated with ~100 molecules to available ligands (n = ~108) in the monolayer.[48] Gibson et al have recently succeeded in coupling of ~70 molecules of paclitaxel, to a gold nanoparticle with 2 nm core diameter.[49]

1.11. Polymersomes:

Polymersomes are hollow shell nanoparticles, having unique properties that allow delivery of drugs. Loading, delivery and cytosolic uptake of drug mixture from degradable polymerosomes were shown to exploit the thick membrane of these block copolymer vesicles, their aqueous lumen, and pH-triggered release with in endolysosomes. Polymerosomes break down in the acidic environments for targeted release of these drugs within target cell endosomes. Ahmed et al have recently investigated on polymersomes to encapsulate paclitaxel and doxorubicin for passive delivery to tumor target site.[50]

Clinical toxicities of nanotechnology-based drug delivery: A challenge

Before the application of nanotechnology-based drug delivery, we need to be aware of the toxicity of ‘nano-deliveries’ resulting from their nanoscale size. Materials in this size-range may approach the length scale where their properties differ substantially from those of bulk materials of the same composition, allowing them exceptional feats of reactivity, for instance. Possible undesirable results of these capabilities are harmful interactions with biological systems and the environment with potential to generate toxicity.[51-53] Therefore, we need to perform a risk-benefit analysis.

Many preclinical studies have already demonstrated a reduced toxicity profile when incorporating and delivery of immunosupressants like rapamycin and cyclosporine etc, as well as anticancer agents like geldanamycin etc, into various nanocarriers in rodent studies.[54-56] The safety of patients and clinicians who will handle these 'nano-deliveries' in the treatment of various diseases in future are of primary concern. Clinical protocols must be established on the handling and delivering nanoparticle-based delivery effectively.

Future prospect of nanotechnology in drug delivery

Nanotechnology facilitates the key to unlocking the innovation of oral delivery peptides, such as oral insulin, other hormones, growth factors, clotting factors, anticoagulants etc to overcome several obstacles like limited bioavailability, inadequate stability, immunogenicity, and limited permeability across the biological membrane. Nanotechnology will soon permit the fusion of peptides with oral, topical, transdermal, and implantable drug delivery systems. Implantable devices or nanochips promise improved therapeutics in various disease management and may be potentially applied as antitumor therapy, gene therapy, or vaccines. Nanochips may even be used to assist in repairing damaged tissue, detecting mutated genes, or detecting high hormone levels indicative of certain malignancies.[57] Nanochips may be capable of triggering immediate responses to inflamed, ischemic, or neoplastic tissues and simultaneously provide therapy. Surprisingly, a silicon based nano-channel has already been developed to deliver antitumor agents locally with zero order kinetics.[58] Nanotechnology propose solutions to the old age problems associated with the solubility, bioavailability, cytocompatibility, immunocompatibility, and cellular uptake of many traditional medications.[59]

CONCLUSION

The nanotechnological field in drug delivery applications has a bright future with the emergence of several promising approaches like dendrimers, solid lipid nanoparticles, polymeric nanoparticles, polymeric micelles, liposomes, nanosuspensions and nanocrystals, ceramic nanoparticles, carbon nanotubes (CNTs), quantum dots (QDs), gold nanoparticles, polymersomes etc. However, the cost of these 'nano-deliveries' should be in acceptable low range to be successful in the clinics. In future, various multifunctional novel nanoparticle-based drug deliveries may be designed and developed. We are optimistic that an increasing number of novel 'nano-deliveries' for drug delivery applications in treatment of various diseases will emerge. We expect that with continued support, drug delivery applications will be an important beneficiary of nanotechnology for years to come.

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