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Review

RECENT ADVANCES IN NANO DRUG DELIVERY AND NANO MEDICINE

Hitesh K Maradiya*[1], Vasundhara H Pansara[2], Vidyasagar G[1]

[1]Veerayatan Institute of Pharmacy, Mandvi- Kutch, Gujarat (India)

[2]Noble Pharmacy College, Junagadh, Gujarat (India)

* Corresponding author

E mail: hitu.pharma87@gmail.com

Abstract

Nanomedicine is the medical application of nanotechnology. Nanomedicine ranges from the medical applications of nanomaterials, to nanoelectronic biosensors, and even possible future applications of molecular nanotechnology.Research in the areas of drug delivery and tissue engineering has witnessed tremendous progress in recent years due to their unlimited potential to improve human health.nano-scale drug-delivery systems include nanoparticles, nanocapsules, nanotubes, nanogels and dendrimers. They can be used to deliver both small-molecule drugs and various classes of biomacromolecules, such as peptides, proteins, plasmid DNA and synthetic oligodeoxynucleotides. Nanocomposites containing nanocrystals have been shown to elicit active bone growth.This review summarizes the most recent development in utilizing nanostructured materials for applications in drug delivery and tissue engineering.in this review to give information about various recent formulation of nano medicine which is used in different treatment for cure of disease like cancer and other benefit of that drug is mainly to gives a very low side effect and law risk in human life.

Key Words: Nanoparticles, Nanocapsules, Nanotubes, Nanogels, Tissue engineering

Introduction

The interdisciplinary field of nanobiotechnology, which combines chemistry, biology, engineering and medicine, is revolutionizing the development of drug-delivery systems and devices.[1] Novel materials and formulations are enabling the site-specific targeting and controlled release of traditional pharmaceuticals, recombinant proteins, vaccines and nucleic acids.Future generation systems will include biosensing functionalities with in vivo feedback that will permit "smart" drug delivery.[2-4] Nano-scale drug-delivery systems can be devised to tune release kinetics, to regulate biodistribution and to minimize toxic side effects, thereby enhancing the therapeutic index of a given drug.[2] Particle size is extremely important to the biological properties and, hence, function, of nano-scale drug-delivery systems.[5] Nano-scale drug-delivery systems take advantage of the fact that nano-scaled materials (10−9 to 10−7 m) can exhibit distinctive physical properties, electrical, mechanical and optical, that differ from those observed in the macroscopic and atomic realms.[6] While spherical nanoparticles are the simplest to create, other shapes and constructions offer advantages for certain applications. These supramolecular systems include nanocapsules, nanotubes, nanogels and dendrimers.

The main overall research objectives currently defined for the area of nanomedicine and drug delivery systems are:

i. Achieving intracellular delivery of nucleic acids and/or combination chemotherapy by the use of nano-systems for cell (cytosolic) specific delivery in oncology and inflammation
ii. Attaining effective mucosal vaccination through micro and nano-systems, as well as design of well suited therapeutic systems for intracellular pathogens
iii. Developing mechanistic and technological innovative approaches for dermal delivery in different conditions such as inflammation, cancer and/or autoimmune diseases
iv. Using innovative approaches using macromolecular complexation and particle engineering for pulmonary delivery, as well as for other non-parenteral routes.

Nanoparticles

Nanotechnology is the design and assembly of submicroscopic devices called nanoparticles, which are 1-100 nanometers in diameter. Nanomedicine is the application of nanotechnology for the diagnosis and treatment of human disease.[7] This section refers specifically to polymer-based matrix particulate systems. Specifically, nanoparticles have been defined as *submicron-sized polymeric colloidal particles with a therapeutic agent of interest encapsulated within their polymeric matrix or adsorbed or conjugated onto the surface*.[8] The drug payload can be released outside of or within the target cells. Drug-delivery systems can be administered locally or systemically, with the potential for the attachment of targeting moieties. While larger drug-delivery systems can create high local drug concentrations, smaller drug-delivery systems can be endocytosed directly.[8] Nanoparticles have even been shown to cross the blood–brain barrier.[9] A variety of materials can be used to synthesize nanoparticles and more advanced chemistries are pending.[10] Recent novel examples, many of which are not polymer-based, include calcium carbonate,[11] calcium- deficient hydroxyapatite,[12] chitosan,- oligo -3-hydroxy butyrates[14] and porous hollow silica.[15]

Gold nanospheres can be prepared easily by the reduction of auric acid with sodium citrate.[16] The size of the nanoparticles can be varied by changing the sodium citrate concentration.[17] Citrate-capped nanoparticles are very stable. In addition, the citrate-capping can be replaced easily and the gold surface can be functionalized with various ligands, such as DNA, peptides and antibodies, by means of covalent and noncovalentinteractions.[18,19] Gold nanorods can be synthesized by the well developed electrochemical method through gold ionization and reduction[20] or the seed-mediated growth method involving the growth of spherical gold seed particles in the presence of Au+ ions and the rod-like cetyltrimethyl ammonium bromide (CTAB) surfactant.[21,22] The aspect ratio (length/width) of the rods can be tuned readily by changing the concentration of the silver ions. The nanorod surface also enables multifunctionalization. In addition to good synthetic control, gold is potentially biosafe. The recent promise of colloidal gold nanoparticles for modernmedicinal applications, especially cancer diagnostics and photothermal therapy, has originated mainly from their strongly enhanced optical properties. Recent *in vitro* studies show that gold nanoparticles do not cause cytotoxicity in human cells.[23]

Nanotubes

Nanotubes can be fabricated from many materials and via distinct routes, ranging from self-assembly to deliberate deposition. Nanotubes, structures that resemble tiny drinking straws, offer advantages over spherical nanoparticles for some applications.[24] Their large inner volumes can be filled with sundry chemicals and biomolecules, ranging in size from small molecules to proteins.[25,26] Because the inner and outer surfaces of certain types of nanotubes are distinct, they can be differentially modified to encapsulate specific drugs internally and to evade immunogenic response externally.[26] Finally, the open-mouthed structure of nanotubes renders loading especially simple. Examples include fullerene carbon nanotubes, cyclic peptide nanotubes and template-synthesized nanotubes.[24] Polymeric nanotubes can be synthesized via in-pore polymerization; metal nanotubes can be produced by electroless deposition; and inorganic nanotubes can be created by sol–gel chemistry.[27]

Recently, nanotube spearing was used to achieve extremely high transfection efficiency with high post-induction cell viability in hard-to-transfect cells, including B cells and primary neurons.[28] This technique uses nickel-embedded nanotubes to penetrate cell membranes via magnetic field driving, thereby delivering macromolecules that are immobilized on the nanotubes. This approach offers several benefits, including increased control, decreased cytotoxicity and greater efficiency than standard transfection reagents.[29,30]

Carbon nanotubes (CNTs) have recently gained popularity in the burgeoning field of nanotechnology. CNTs possess high aspect ratio with nano diameter and can beclassified into two types: (i) single-walledcarbon nanotubes (SWCNTs; Fig. 1) consisting of a single layer of grapheme sheet (a single atomic layer of graphite) seamlessly rolled into a cylindrical tube and (ii) multi-walled carbon nanotubes (MWCNTs; Fig. 1) comprising two or more layers of concentric cylinders witha separation of about of 0.34 nm betweenthe adjacent layers.[31,32]

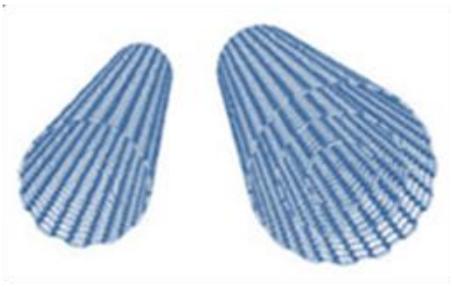

Fig. 1. Molecular structure of SWCNT (left) and MWCNT (right)

Despite the revelations that the exposure to pristine CNTs is harmful, functionalized (chemical modification) CNTs (f-CNTs) are employed both in the treatment of cancer and as drug-delivery vehicles at the target without any toxic effects. While biological systems are transparent to 700–1100 nm near-infrared (NIR) light, the strong optical absorbance of SWCNTs in this region has been exploited to destroy cancer cells.[33] Selective ablation of tumour cells can be achieved by functionalization of SWCNTs with a folate moiety, selective internalization of SWCNTs inside cells labeled with folate receptor tumour markers, and exposure to noninvasive NIR, without harming receptor-free normal cells.

Nanocapsules

Lipid and polymeric nanocapsules are nano-scale drug-delivery systems that can provide controlled release and efficient targeting.[34,35] The composition of the outer coating, in particular, dictates their dispersion stability and the primary physiological response.[34] The fabrication of nanocapsules can be achieved by interfacial deposition, interfacial polymerization, interfacial precipitation, layer-by-layer deposition and self-assembly procedures. Important variables include capsule size, radius distribution, capsule thickness, membrane decomposition and surfactant type.[35] Cisplatin-to-lipid molar ratio and exhibit greatly improved cytotoxicity against tumor cells in vitro relative to free drugs.[36] Still, the use of lipids can be limited by their instability in biological media and by their sensitivity to many external parameters, including temperature and osmotic pressure.[37]

A recent advance in the pursuit of a biocompatible nanocapsule has been the use of *the vault*, a naturally occurring cellular nanoparticle thus named for its morphology.[38] Another interesting development was the synthesis of disulfide cross-linked polymer capsules.[39] The disulfide bonds confer enhanced stability to hydrogen-bonded multilayer thin films at physiological pH. They also render the system susceptible to disassembly in the presence of thiol–disulfide exchange reagents. Accordingly, these nanocapsules have the potential to be used as biodeconstructible nano-scale drug-delivery systems, as intracellular proteins, such as glutathione, will promote *in vivo* capsule deconstruction[40,41] (Fig. 2).

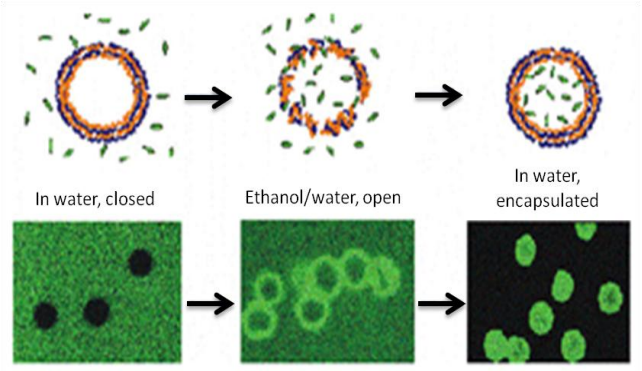

Fig. 2. Biodegradable nanocapsules

As naturally-occurring, non-immunogenic, protein-based nanoscale capsule, the vault particle has the potential to serve as a flexible therapeutic delivery vehicle. Engineered in the baculovirus system, the particle self-assembles from a single expressed protein which can be modified to allow cell targeting, specific endocytosis and endosome penetration.[42-45] The CCL21-vault nanocapsule platform is an effective antitumor strategy. This holds significance for broad application as an off the shelf reagent for cancer therapy. We have demonstrated that vault nanoparticles containing the major outer membrane protein of Chlamydia, could be delivered to the respiratory tract, by the intranasal route and induced robust anti-chlamydial immune responses.[42] The addition of EGF onto the outside of vault particles can be used to specifically target cells expressing high levels of EGFR and leads to phosphorylation of Tyr1173 on the

receptor.[45] This suggests that vault particles can be designed as multifunctional vehicles that can be further engineered for target specific delivery as well as carriers of specific payloads that can act as tumor antigens to prime the immune system to potentially act as vaccines to prevent tumor recurrence and metastasis. These multifunctional nanoparticles may prove indispensable as cancer therapeutics. The results of our study are encouraging and warrant further evaluation of the vault nanocapsule delivery platform for its full therapeutic potential in lung cancer and other malignancies.

Nanogels

Generally, the drug is subsequently loaded via self-assembly processes based on non-covalent interactions. Both charged and hydrophobic biomolecules can be incorporated into hydrogel networks, which are themselves characterized by the physical properties of their constituent polymers.[46] Hydrogels are hydrophilic, three-dimensional cross-linked polymer networks that swell in the presence of water.[46,47] Nano-scale hydrogels, or nanogels, offer straightforward synthesis and relatively high drug-loading capacity.[46] They can be designed to respond to many physiological stimuli, including ionic strength, pH and temperature.[46,47] Hybrid polymerizable nanogels that incorporate both physical and chemical cross-linking structures have been synthesized.[48] Nanogel particles combine the properties of gels with the properties of colloids: high surface-to-volume ratio, micro heterogeneous structure and small size. Hydrogels can been coated with lipids to preserve colloidal stability, these procedures are limited by low coating efficiency.[49-51] A degradable gel is surrounded by a membrane that is permeable to water but impermeable to the drug and the gel-degradation products. Gel degradation increases swelling pressure, resulting in membrane rupture and drug release. Self-exploding microgels were recently created for the purpose of pulsed drug delivery.[49,52]

Nanogel is also formulated by Self-assembly of surfactant molecules into micelles of various shapes and forms has been extensively used to synthesize soft nanomaterials. Translucent solutions containing rod-like surfactant micelles can self-organize under flow to form viscoelastic gels. This flow-induced structure (FIS) formation has excited much fundamental research and pragmatic interest as a cost-effective manufacturing route for active nanomaterials. However, its practical impact has been very limited because all reported FIS transitions are reversible because the gel disintegrates soon after flow stoppage. We present a new microfluidics-assisted robust laminar-flow process, which allows for the generation of extension rates many orders of magnitude greater than is realizable in conventional devices, to produce purely flow-induced permanent nanogels. Cryogenic transmission electron microscopy imaging of the gel reveals a partially aligned micelle network. The critical flow rate for gel formation is consistent with the Turner–Cates fusion mechanism, proposed originally to explain reversible FIS formation in rod-like micelle solutions.[53]

Novel systems

Novel nano-scale drug-delivery systems that explore original applications of structures, shapes, materials and phase boundaries are being developed. The following systems represent some recent advances from the literature. Biodegradable implantable nano-scale drug-delivery systems have also been fashioned. Polymeric nanofibers with controlled surface and internal molecular structures can be produced by electrospinning to yield scaffolds for controlled drug release. A silicon-based nanochannel was constructed to deliver anti-tumor compounds locally to unresectable tumors with zero-order kinetics.[54,55] The device can be implanted using a minimally-invasive procedure to overcome the inconvenience of frequent local injections.

Specifically, nanoparticles can be coated with polymeric nano shells via layer-by-layer stepwise self-assembly.[56] Standard nanoparticles can be altered to create more complex structures. The nano shell provides a template upon which surface modifications can be made to create stealth or targeted nano-scale drug-delivery systems. Nanoparticles can also be formulated to address delivery route-specific needs. Nanoparticles have been formulated as microparticle agglomerates with cleavable in vivo chemical cross-linkages to achieve post-inhalation modulation of pulmonary drug-release rates.[57] Nano-scale drug-delivery systems, combined with the ability to control architectures, to create novel materials and to customize formulations, will enable engineers, scientists and physicians to exploit nanotechnology for advanced applications in drug delivery.

In Novel system as nanobots are robots that carry out a very specific function and are just several nanometers wide. They can be used very effectively

for drug delivery. Normally, drugs work through the entire body before they reach the disease affected area. Using nanotechnology, the drug can be targeted to a precise location which would make the drug much more effective and reduce the chances of possible side-effects. Nanomedicine is the medical application of nanotechnology. The approaches to nanomedicine range from the medical use of nano materials, to nano electronic biosensors, and even possible future applications of molecular Nanomedicine research is directly funded, with the US National Institutes of Health. Particulate novel systems like nanoparticles have been as physical approach to alter and improve the pharmacokinetic and pharmacodynamic properties of various types of drug molecules. Particle size and surface characteristic of nanoparticle can be easily manipulated to achieve both passive and active drug targeting after parental administration. They have been used in vivo the drug entity in the systemic circulation, restrict access of the drug to the chosen sites and to deliver drug at a controlled and sustained rate to the site of action.[58-61]

Dendrimers

Dendrimers are generally roughly spherical molecules with very well defined size and shape (Fig. 3). This physical characteristic, combined with their thermally decomposable organic nature, makes them especially suitable for use as porogen (a pore-generating material). This can be applied in the creation of foams with optimized nanoscale poresizes and distributions, such as synthetic zeolites for catalysis or low dielectric constant materials (in simple terms, good insulators) for use in ever-shrinking integrated circuits. They have also been used as templates to obtain larger structures with particular characteristics. Recently, the first example of the formation of amorphous calcium carbonate by artificial methods was reported. Dendrimers are very flexible structures. When secondary interactions are introduced into the system, dendrimers have the ability to completely change their conformation to form layers or even self-assembled lipid-like structures. They can transform their shape from spherical to almost completely flat, if the interactions with the surface are adequate.[62]

Dendrimer synthesis, which has recently been simplified, can be achieved by the divergent lego approach or by the convergent click approach.[63] Both strategies permit easy purification and produce environmentally-safe byproducts. The former route requires only one step per generation.[64] The latter route, based on the Cu(I)-catalyzed synthesis of 1,2,3-triazoles from azides and alkynes, yields dendrimers with various surface groups in high purity and excellent yield.[65] Most dendrimeric drug delivery has focused on chemotherapeutic agents, including cisplatin, methotrexate and 5-fluorouracil,[66] affording slower release, greater accumulation in solid tumors and decreased systemic toxicity than free drugs, particularly when the dendrimer is PEGylated. Dendrimers with positively-charged surface groups are apt to destabilize cell membranes, causing lysis. Amino-terminated PAMAM (poly amido amine) dendrimers do, however, exhibit lower toxicity than more flexible amino-functionalized linear polymers.[67] Primary amines are more toxic than secondary or tertiary amines. As mentioned, surface functionalization, particularly with PEG, can reduce cytotoxicity. Still, dendrimers can only be regarded as safe in relation to a specific application: limited clinical experience with dendrimers render safety generalizations about given chemistries difficult.[68]

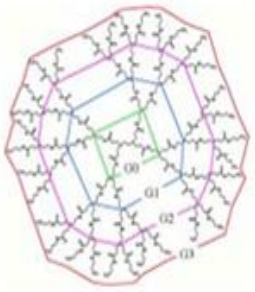

Fig. 3. Structure of dendrimer

Novel dendrimeric systems for applications as nano-scale drug-delivery systems include biaryl-based dendrimeric micelles that exhibit environment-dependent conformations,[69] bow-tie architectures that covalently connect a drug-loaded dendron to a PEGylated, solubilizing dendron[70] and hybrid dendrimer-based microcapsules that enable a dual release scheme. In addition to serving as drug-delivery vectors, dendrimers can act as inherently-active antitumor, antiviral and antibacterial agents and as permeability enhancers that can promote oral and transdermal drug delivery.[71,72]

Polymers

Polymer therapeutics comprises rationally-designed macromolecular drugs, polymer–drug and polymer–protein conjugates, polymeric micelles and polyplexes for DNA delivery.[73] The greatest advantage of these species is their amenability to

chemical modification, resulting in defined chemical composition, customized surface functionality and the potential for defined three-dimensional structures.[73] Drugs can be physically entrapped within polymer shells and matrices, or they can be covalently attached to the polymer backbone. Polymer–drug conjugates, which contain a systemically-stable, bioresponsive polymer–drug linker, alter the pharmacokinetics of the drug by increasing the drug's effective molecular weight.[74] Polydispersity is of particular importance because biological properties are molecular weight dependent. Because polymers are often internalized by cells, biocompatibility is another area of concern.[75]

Scientists continue to explore new biodegradable polymers that exhibit more sophisticated three-dimensional structures[36] and are better suited to frequent parenteral administration.[76]

The transition from micro- to nano-particles leads to change in the physical as well as chemical properties. Two of the major factors in this are the increase in the ratio of the surface area to volume, and the size of the particle. The increase in surface area-to-volume ratio, which increases as the particles get smaller, leads to an increasing dominance of the behavior of atoms on the surface area of particle over that of those interior of the particle. This affects the properties of the particles when they are reacting with other particles. Because of the higher surface area of the nano-particles, the interaction with the other particles within the mixture is more and this increases the strength, heat resistance, etc and many factors do change for the mixture. An example of a nanopolymer is silicon nanospheres which show quite different characteristics; their size is 40-100 nm and they are much harder than silicon, their hardness being between that of sapphire and diamond. Due to the large number of natural or synthetic polymers available and the advanced techniques developed to process such systems to nanofibres, rods, tubes etc make polymers a good platform for the immobilization of biological objects.[77]

Conclusion

Nano medicine and drug delivery is recent technology that can be used to achieve specific systemic delivery in human body. The main advantages of this nano medicine and nano particles are less side effects and faster pharmacological effects. The nanoparticles are easy to prepare and potentially biosafe. Hence, in years to come, nano drug delivery systems will be the most preferred drug delivery systems to cure various diseases.

Declaration of Interest

It is hereby declared that this paper does not have any conflict of interest.

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