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NANO FABRICATED DRUG DELIVERY DEVICES

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Abstract

Nanotechnology is novel branch of science that deals with the characterization, creation, and utilization of materials, devices, and systems at the nanometer scale. Advances in nanotechnology are spurring a revolution in science, engineering and therapeutics, particularly in drug delivery. Targeted delivery of therapeutic molecules is the most desirable feature of an effective drug therapy. Conventional chemotherapy faces major drawbacks such as poor specificity of the drug, increased adverse effects, and reduced therapeutic efficacy. Application of nanotechnology in drug delivery systems has provided new avenues for engineering materials with molecular precision. This aids in fabricating nanoscale delivery devices that combine diagnostic and therapeutic actions for immediate administration of therapy. Nanotechnology can generate a library of sophisticated drug delivery systems that integrate molecular recognition and site-specific delivery of the therapeutic agents. It formulates therapeutic agents in biocompatible nanomaterials such as nanoparticles, nanocapsules, and micelles.

Presently pharmaceutics primarily consists of simple fast acting chemical compounds that are dispensed orally (as solid pills and liquids) or as injectables. During the past three decades, however, formulations that control the rate and period of drug delivery (i.e., time-release medications) and target specific areas of the body for treatment have become increasingly common and complex. Because of ever-evolving understanding of the human body and the explosion of new and potential treatments resulting from discoveries, pharmaceutical research hangs

on the precipice of yet another great advancement. However, this next leap poses questions and challenges to not only the development of new treatments but also the mechanisms with which to administer them.

The goal of all sophisticated drug delivery systems, therefore, is to deploy medications intact to specifically targeted parts of the body through a medium that can control the release or administration by means of either a physiological or chemical trigger. To achieve this goal, researchers are turning to advances in the worlds to micro- and nanotechnology.

Key words: Nano, drug delivery, nanotechnology, targeted delivery.

Introduction

The application of nanotechnology for treatment, diagnosis monitoring and control of biological systems is referred to as 'Nano medicine', by National Institute of Health.[1] The essential difference between micro and nanoparticles is not merely the size but also the ability of nanoparticles to achieve higher drug encapsulation and enchance the bioavailability of orally administrated drugs. Nano particles are known to cross intestinal permeability barrier directly via trancellular/paracellular pathways that explains the better delivery of encapsulated drugs into the circulation.[2, 3]

Nano drug delivery system can lower systemic drug toxicity, improving treatment absorption rates, and providing protection for drugs against biochemical degradation. Also to fabricate nanoscale core shell particles, by which poor water soluble drugs can be effectively dispersed with rather good stability during storage[4].

The drug targeting can be achieved by the local administration of the therapeutic compounds; this strategy is feasible even with conventional dosage forms. For example, if the site for desired drug action is the skin, the medication may be applied in ointment, lotion or cream, directly on the desired site. But sophisticated drug targeting technologies are concerned with delivering drugs to specific targets in the body and also to protect drugs from degradation and premature elimination[5].

Efforts in the 1970s and 1980s allowed rational design (bearing in mind the proposed use and pathophysiology of the disease target [6]. Study of various methods used to carry the drugs to the specific targets such

as polymeric micelles was done by Nishiyama and Kaooka[7]. Similarly Heparin-deoxycholic acid chemical conjugate was used as anticancer drug carrier at nano ranges (180-210 nm) by Kyeongsoon Park et al[8]. Martha Kalkanidis[9] used nano particles based inert (40 nm) solid carrier beads to which antigen was covalently coupled to deliver vaccines. Jun Watanable et al[10] studied about entrapment of compounds into bio compatible nano sized particles and their releasing properties.

The need for research into drug delivery system extends beyond ways to administer new pharmaceutical therapies; the safety and efficacy of current treatments may be improved if their delivery rate, biodegradation, and site-specific targeting can be predicted, monitored, and controlled. From both, financial and a global health care perspective, finding ways to administer injectable-only medications in oral form and delivering costly, multi-dose, long-term therapies in inexpensive, potent, and time-releasing or self-triggering formulations are also needed. The promise of administration methods that allow patients to safely treat themselves is as significant as any other health care development, particularly in developing countries where doctors, clean syringes, sterile needles, and sophisticated treatments are few and far between.

Various chemical routes are used to prepare the desired nano materials. Nanoparticles have become an important area of research in the field of drug delivery because they the ability to deliver a wide range of drugs to different areas of the body for sustained period of time. The small size of nanoparticles is integral for systemic circulation. Natural polymers have not been widely used for this purpose since they vary in purity, and often require crosslinking that could denature the embedded drug. Consequently synthetic polymers have received significantly more attention in this area. The most widely used polymer for nanoparticles have been poly caprolactone (PCE), poly lactic acid (PLA), poly glycolic acid (PGA) and their co-polymers[14] in addition block co-polymers of PLA and poly ethylene glycol (PEG) and poly amino acids have been used to make nanoparticles and micelle like structures[14]. These polymers are known for their bio compatibility and reabsorptivity through natural pathways. Additionally the degradation rate and accordingly the drug release rate can be manipulated by varying the ratio of PLA or PCL, increased hydrophobicity, to PGA, and increased hydrophilicity.

Nanoparticles such as liposomes, micelles, worm-like micelles, polymersomes and vesicles have also been proposed recently in the literature as promising drug delivery vehicles because of their small size and hydrophilic outer shell. Nanoparticles can be used to deliver hydrophilic drugs, hydrophobic drugs, proteins, vaccines, biological macromolecules[14]. They can be formulated to targeted delivery specific organs for long term systemic circulation. Therefore numerous protocols lost for synthesizing nanoparticles based on the type of drug used delivery route. Once a method is chosen parameters must be tailored to create the best possible characteristics of the nanoparticles. Four of the most important characteristics of nanoparticles are their size, encapsulation efficiency, zeta potential, and release characteristics.

The researches at University of Texas at Austin have described a means of using nanospheres for oral drug delivery.These nanospheres carriers are derived from hydrogels, which are highly stable organic compounds that swell when their environment becomes more acidic. They have been successfully formulated into controlled release tablets and capsules, which release active compounds when hydrogel body swells.

Results and Discussions

Different carrier systems are currently being evaluated including polymers, dendrimers, sol-gel coatings, or other porous inorganic materials. Nano materials and devices can be fabricated using either “bottom-up” or “top-down” fabrication approaches. Controlled drug-delivery strategies have made a dramatic impact in medicine. In general, controlled release polymer systems deliver drugs in optimum dosage for long periods, thus increasing the efficacy of the drug, maximizing patient compliance and enhancing the ability to use highly toxic, poorly soluble or relatively unstable drug. These vehicles can be engineered to recognize biophysical characteristics that are unique to the target cells and therefore minimizing drug loss and toxicity associated with delivery to non-desired tissues.

In general, target nanoparticles comprise the drug, the encapsulating material and the surface coating. The encapsulating material could be made from biodegradable polymers, dendrimes orliposomes. Controlled release of encapsulation material is achieved by the release of encapsulated drugs through surface or bulk erosion, diffusion, or triggered by the external environment, such as change in pH, light, temperature or by the presence of analytes

such as glucose[14]. Controlled release of biodegradable nanoparticles can be syntheized from wide variety of polymers including poly lactic acid, poly glycolic acid, poly lactico-glycolic acid, polyanhydride. Since poly glycolic acid is more susceptible to hydrolysis than poly lactic acid, by changing the ratio of these two components, co-polymers can be synthesized with various degradation rates. We have to look into the areas of improving the properties of the materials such as bio compatibility, degradation rate and control over the size and homogeneity of the resulting nanoparticles.

Synthesis of solid nanoparticles

The most common method used for the preparation of solid, polymeric nanoparticles is the emulsification-solvent evaporation technique. This technique has been successful for encapsulating hydrophobic drugs, but has poor results in incorporating bioactive agents of a hydrophilic nature. Briefly solvent evaporation is carried out dissolving the polymer and the compound in an organic solvent. The emulsion is prepared by adding water and a surfactant to the polymer solution. In many cases, nano-sized polymer droplets are induced by sonification or homogenization. The organic solvent is evaporated and the nanoparticles are usually collected by centrifugation and lyophilization.

Processing parameters

Consideration should be given for the selection of compound used in the nanoparticles production including the polymer molecule weight of the polymer, the surfactant, the drug and the solvent. For example, different surfactants may produce particles of different sizes. An increase in the molecular weight will cause an impact on the release rate from the particles causing slower pore formation within the particles and therefore slower release. Other processing variables include the time of emulsification, the amount of energy input, the volume of sample being emulsified. As energy input in the emulsion increases, the resulting particle size decreases. In addition there are four separate concentrations that can be altered: the polymer, drug, surfactant and solvent. Often, a low concentration of surfactants will result in a high degree of poly dispersity and aggregation. Finally, the recovery of the particles can be changed depending on the method of lyophilization or centrifugation.

Characterization

Size and Encapsulation efficiency

When considering polymeric nanoparticles for a given drug delivery application, particle size and encapsulation efficiency are two of the most important characteristics. For rapid dissolution in the body or arterial uptake, then size of the nanoparticles should be approximately 100 nm or less. If prolonged dissolution is required, or targeting the mono- nuclear phagocytic system, longer particles around 800 nm required. The encapsulation efficiency increases with the diameter of the nanoparticles. The molecular weight of the polymer has opposite effect on nanoparticle size and encapsulation.

Zeta potential

The zeta potential is a measure of the charge of the particle, the relation being that the larger the absolute value of the zeta potential, the larger amount of charge of the surface. As the zeta potential increases, the repulsive interactions will be larger leading to the formation of more stable particles with a more uniform size distribution.

Surface Modification

It should be considered what is the nature of the drug as well as the means and duration desired for the delivery. That will determine not only how the particles are synthesized but also what the nature of particles should be.

Nanoparticulate delivery system

Polymeric micelles can be assembled from block co-polymers composed of hydrophobic and hydrophilic segments. The hydrophobic segment creates the inner core of the micelle, while the hydrophilic segment creates the outer shell in an aqueous media. Polymeric micelles can be used as a drug delivery device by either physically entrapping the drug in the core or by chemically conjugating the drug to the hydrophobic block prior to micelle formation. Drugs either physically of chemically trapped in the hydrophobic core are protected from chemical degradation, minimizing unwanted side effects. Micelles have several benefits as drug delivery vehicles. Their hydrophilic outer shell and small size (<100 nm) renders these particles nearly invisible to the reticuloendothelial

system, allowing for long term circulation in the bloodstream. Furthermore, micelle stability is relatively high due to the fact that, unlike other aggregates for drug delivery such as vesicles, they are a thermodynamically equilibrium aggregate.

Application of Nanotechnology in treatment of Cancer

Cancer is one of the most challenging diseases today and brain cancer is one of the most difficult malignancies to detect and treat mainly because of the difficulty in getting imaging and therapeutic agents across the blood-brain-barrier (BBB), many new chemical entities have proved not to be clinically useful. Nanoparticles have been demonstrated to cross the BBB with little difficulty and companies such as Germany's Nanopharm have developed systems capable of reaching the brain for ananthesia(Dalargin; an analgesic). The company claims several advantages over existing system's, including no need to modify drug itself and its ability to deliver potentially any drug whether hydrophillic or hydrophobic.

Mechanistic perspectives for 1,2,4-trioxanes in anti-cancer therapy was evaluated by Thomas Efferth[11]. The biomolecular binding behavior of anticancer drug dacarbazine in the presence of titanium dioxide nanoparticle was studied by Min Song et al[12]. The results indicate that the presence of TiO_2 nanoparticles can obviously increase the binding affinity of dacarbazine to DNA or DNA bases and significantly enhance the detection sensitivity for the relative biomolecular recognition. Mina Nikanjama[13] synthesized nano low density lipoprotein as targeted drug delivery vehicle for glioblastoma multiforma. The particles were constructed by combing a synthetic peptide containing binding motif and the LDC receptor binding domain of apolipoprotein with a liquid emulsion consisting of phosphatidylcholine, triolein and cholesteryl oleate.

Conclusion

Nano drug delivery systems hold great potential to overcome some of the barriers for efficient targeting of cells and molecules in the cancer. The challenge however remains in the precise characterization of molecular targets and to ensure that these molecules are expressed only in the targeted organs to prevent effects on healthy tissues. Furthermore, because nanosystems increase efficiency of drug delivery, the doses may need recalibration[15].

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