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Nanotechnology Based Drug Delivery System and its Applications

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ABSTRACT

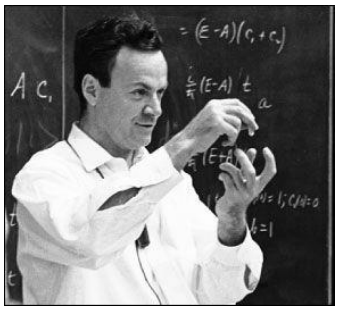
Nowadays, nanotechnology is considered as one of the most wide spread field of science with its important application in different fields as health, biology, chemistry, etc. in this review article we will discuss applications of nanotechnology in the field of health care, different used techniques and some examples.

Nanotechnology, in a blink.

The definition of nanotechnology is typically stated in **Bhushan (2010)** "Nanotechnology literally means any technology on a nanoscale that has applications in the real world. Nanotechnology encompasses the production and application of physical, chemical, and biological systems at scales ranging from individual atoms or molecules to submicron dimensions, as well as the integration o the resulting nanostructures into larger system."

Applications of nanotechnology are very wide and can be found in many fields as biology, chemistry, physics, agriculture, medicine and engineering.Because the field of nanotechnology depends mainly on manipulating and controlling molecules in the atomic level, the field of nanoscience starts to thrive by the invention of the microscope that can magnify molecules and atoms almost 30 years ago.

Historical point of view



The American physicist **Richard Feynman (1918-1988),** was the first scientist who pointed out to nanotechnology and nanoscience in his memorial talk "There's Plenty of Room at the Bottom" in American Physical Society meeting at the California Institute of Technology (CalTech) on December 29, 1959. His talk was published in 1960. In **Richard Feynman (1960)** talk, he discussed a process where scientists can control materials in the atomic level.

Application of nanotechnology in healthcare

Nowadays, all scientists are trying to apply the field of nanotechnology to promote the health status of human being. Nanomedicine is considered as the nanotwchnology application in the field of healthcare. By some techniques they try to improve the behavior and solubility of drug substance and targeting drug material to the site of action in order to minimize possible side effects. So, nanomedicines can assure that the desired quantity of active pharmaceutical ingredient enters the body and react in the specific site of action.

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Nanoparticles, a mean of targeted drug delivery system

Some active pharmaceutical ingredients may not have a good solubility in biological fluids or with badbioavailability. Also some drugs may have some severe side effects if given systematically. So, loading those active ingredients into a designed nanoparticle may help in improving their solubility, increase bioavailability or targeting the drug to the desired site of action and minimize the side effect as much as possible.

Among the techniques used in nanoparticles formation is: micelles, liposomes, virosomes, nanocrystals and nanoemulsion.

Micelles:

A micelle is an aggregate of surfactant where the outer shell is the hydrophilic (lipophobic) part and the inner core is the lipophilic (hydrophobic) part as illustrated in fig. (1). Nanomicelles are particles dispersed in liquids in order to help in the solubilization and targeting of poorly soluble, lipophilic active ingredients. Normally, micelles are spherical in shape. But other shapes maybe occurred as cylindrical or bilayered.

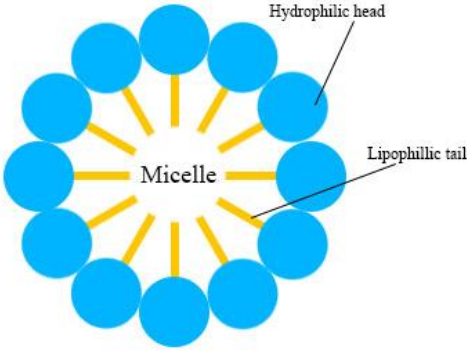

Fig.(1): Spherical micelle

VISUDYNE® (verteporfin) for Injection manufactured by Novartis and approved by FDA in April 2000 , is considered as one of the applications of nanoparticle drug delivery system. Where Vertoporfin is solubilized by nanomicelle formation.

Liposomes:

Liposomes are spherical bilayer aggregates, where the center of the particle is hydrophilic as the shell structure with some lipophillic tails in between. Fig. (2). They can be used as a carrier for transferring drugs or nutrients on aqueous status.

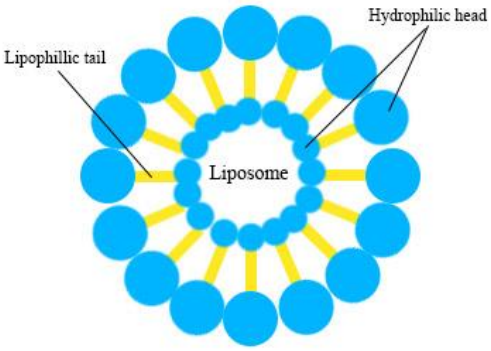

Fig. (2): Liposome

AmBisome® (amphotericin B) Liposome for Injection, manufactured by AstellasPharma/ Gilead is considered as one of the examples of Liposomes. It was approved by FDA in Aug. 1997.

AmBisome is a true single bilayer liposomal drug delivery system. Liposomes are closed, spherical vesicles created by mixing specific proportions of amphophilic

substances such as phospholipids and cholesterol so that they arrange themselves into multiple concentric bilayer membranes when hydrated in aqueous solutions.

Virosomes:

Where a virus deprived protein with its antigens are used in order to transfer a drug material or a vaccine into the cell. Influenza virus vaccine is a good example for virosomes dispersed in suspension.

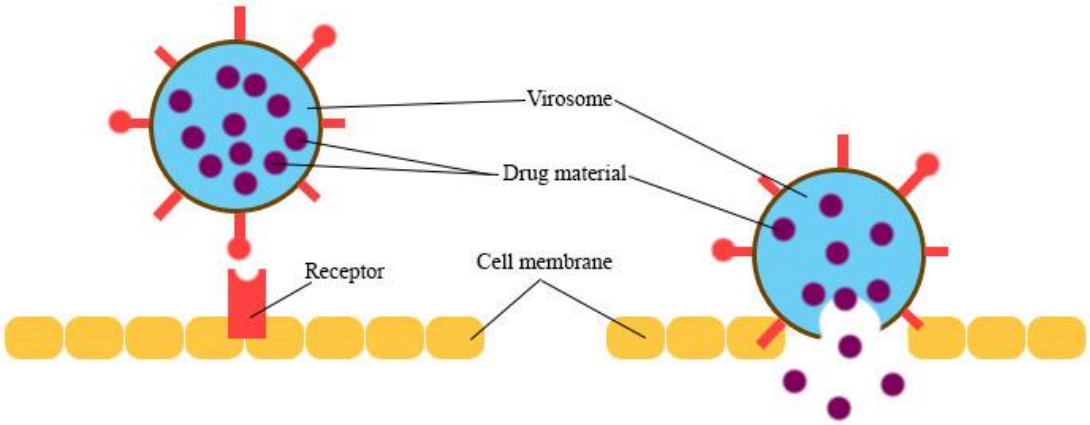

Fig. (3): Virosome attachment with cell membrane.

Nanoemulsions:

"Nanoemulsions are biphasic dispersion of two immiscible liquids: either water in oil (W/O) or oil in water (O/W) droplets stabilized by an amphiphilic surfactant. These come across as ultrafine dispersions whose differential drug loading; viscoelastic as well as visual properties can cater to a wide range of functionalities including drug delivery" as stated by **Yuvraj Singh et al. (2017).**

Fig. (4): Nanoemulsion

Nanocrytals:

Drug nanocrystals are crystals with a size in the nanometer range, which means they are nanoparticles with a crystalline character. There are discussions about the definition of a nanoparticle, which means the size of a particle to be classified as a nanoparticle. Based on the size unit, in the pharmaceutical area nanoparticles should be defined as having a size between a few nanometers and 1000 nm (=1 μm);

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microparticles therefore possess a size of 1–1000 μm according to **Jens-Uwe A H Junghanns & Rainer H Müller (2008)**

A further characteristic is that drug nanocrystals are composed of 100% drug; there is no carrier material as in polymeric nanoparticles. Dispersion of drug nanocrystals in liquid media leads to so called "nanosuspensions" according to **Jens-Uwe A H Junghanns & Rainer H Müller (2008)**.

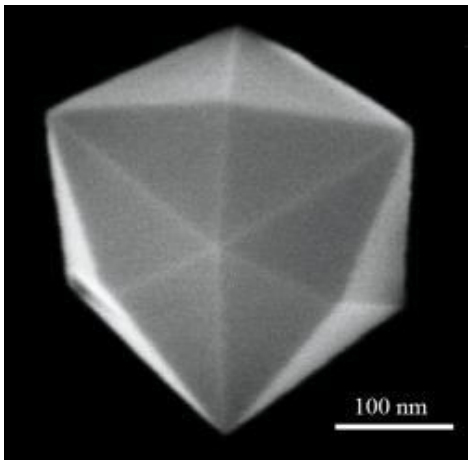

Fig. (5): Nanocrystal

Nanocrystals provide special features including enhancement of saturation solubility, dissolution velocity and adhesiveness to surface/cell membranes according to **Varaporn Buraphacheep Junyaprasert & BoontidaMorakul (2015)**

One of the examples of nanocrystals formation is formulation of Fenofibrate in the form of nanocrytals in order to overcome it's the poor solubility nature and increase its bioavailability.

Application of nanotechnology in drug delivery system:

Targeting Levodopa to the brain of Parkinson's disease patient:

According to **J Jankovic (2008),** Parkinson's disease (PD) is a progressive neurological disorder characterised by a large number of motor and non-motor features that can impact on function to a variable degree. There are four cardinal features of PD: tremor at rest, Rigidity, Akinesia (or bradykinesia) and Postural instability. In addition, flexed posture and freezing (motor blocks) have been included among classic features of Parkinsonism.

Currently, the gold standard of treatment for PDremains the oral administration of dopamine agonists such aslevodopa. Although levodopa provides the greatest benefit formotor symptoms, it is unable to stop or compensate for thecontinual loss of dopamine neurons. Furthermore, the effectivenessof levodopa fades rapidly; and its long-term use often results inserious motor fluctuations according to **Howard E. Gendelman et al. (2015).** In recent years, nanotechnology has been employed in an effort to enhance the efficacy of PD therapy. Major advantages ofusing nanosystems as drug delivery agents include specificdelivery for targeted action in the CNS, effectively overcomingbarriers to CNS, and improving the bioavailability andtherapeutic efficacy of anti-parkinsonian agents. One specificexample of nanotechnology in advanced experimental treatmentof PD is the brain-targeted delivery of dopamine. Using anintracranial nano-enabled scaffold device implantable

in theparenchyma of the frontal lobe of the brain, Pillay and colleaguesshowed that the inclusion of dopamine-loaded cellulose acetatephthalate NPs into a binary cross-linked alginate scaffoldfacilitated local dopamine delivery in a rat model according to **Pillay S et al. (2009).**

Recently,systemic delivery of dopamine has been developed. Trapani et alfound that dopamine-loaded chitosan NPs were less cytotoxicthan free dopaminein vitro. In vivobrain microdialysisexperiments in rats demonstrated that intraperitonealadministration of the dopamine-loaded chitosan NPs effectivelyincreased striatal dopamine levels according to **Trapani A et al. (2011) & De Giglio E et al. (2011).**

In a very recent study,Rashed et al attempted to use polyvinylpyrrolidone-poly (acrylicacid) (PVP/PAA) nanogels synthesized byγ-radiation-inducedtemplate polymerization to systemically deliver dopamine to thebrain according to **Rashed ER et al. (2014).** Nanodelivery of dopaminergic agonists like levodopa, apomorphine, ropinirole and bromocriptine is being pursued also because of the potential to improve brain uptake and reduce side effects associated with these compounds. Levodopa methyl ester, a highly soluble pro-drug that is hydrolysable by plasma esterases, was encapsulated with benserazide in poly (lactic-co-glycolic acid) (PLGA) NPs. This method of administering levodopa successfully abolished levodopa-induced dyskinesia in rats according to **Yang X et al. (2012).**

More recently, intranasal delivery oflevodopa NPs has been explored Levodopa encapsulated in chitosan NPs was incorporated in a thermo-reversible gelprepared using Pluronic PF127, and then delivered viaintranasal route, which increased drug levels in the brain according to **Sharma S et al. (2014).**

Polymeric nanoparticles for improving the bioavailability of Celecoxib:

Referring to **Paulson SK et al. (2001),** Celecoxib is a cyclooxygenase-2 (COX-2) inhibitor used in the treatment of osteoarthritis and rheumatoid arthritis.Also, it has been used in anticancer therapy according to **Van Wijngaarden J et al. (2007).**
Celecoxib is classified as BCS (Biopharmaceutics classification system) Class II, with low solubility and high permeability. So, they tried to modify a drug/polymer nanoparticle in order to increase the molecule bioavilability.

Amorphous drug/polymer nanoparticles containing celecoxib were prepared using ethyl cellulose and either sodium caseinate or bile salt.The experiment shows a promising results, where Nanoparticles dosed orally in aqueous suspensions provided higher systemic exposure and faster attainment of peak plasma concentrations than commercial capsules, with median time to maximum drug concentration (Tmax) of 0.75 h in humans for nanoparticles vs. 3 h for commercial capsules. Nanoparticles released celecoxib rapidly and provided higher dissolved-drug concentrations than micronized crystalline drug. Nanoparticle suspensions are stable for several days and

can be spray-dried to form dry powders that resuspend in water according to **Michael Morgen et al**. **(2012).**

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