International Conference on Research, Innovations and Practices in Science Technology and Management for Societal Benefits
Poddar International College, Tagore Lane, Mansarovar, Jaipur, Rajasthan
Date: 08th - 09th April 2022
ISBN : 978-93-91535-30-8

Peptide-Nanoparticle conjugation and its applications

Khushboo Gautam

Department of Zoology, Poddar International College, Jaipur

Email: khushboogautam550@gmail.com

Abstract:

Drug designing refers to the study of process of using small organic molecules that either activates or inhibits the function of biomolecules, their effects, modification, detoxification, metabolization and elimination by organisms. Drugs are designed based on their interaction with their targeted biomolecule. The targeted biomolecule can be a protein which is non-functional in the body. Identifying the targeted biomolecule is the first step in the process of drug designing in order to find the organic molecule which can bind to it to either enhance or neutralize its effect. Whereas, peptide-based drug designing includes conjugation of peptide-nanoparticles. Nano-peptides are the peptide-based nanomaterials consisting of small peptide sequences, these nanoparticles have several advantages such as high compatibility, high biological activity, bio functionality and are highly modifiable. These peptide-based nanoparticles are therefore have been used in drug-designing and delivery system. They act as nanocarriers for the materials which need to be delivered to the targeted site more efficiently with lesser risk of side effects. These nano-peptides are easily synthesized by selecting amino acids at molecular levels by using basic units in a solid-phase peptide device. Some of the basic advantage of this type of drug-designing and delivery system includes high biological activity, easy injectability, high drug loading capacity, specific targeting. In this review we are going to discuss about the peptide-nanoparticles conjugate based drug designing and delivery system and in its application in molecular imaging.

Keywords: *Drug; Nano-peptides; peptide-nanoparticle conjugation; targeted drug delivery; drug designing; molecular imaging.*

Introduction:

Before moving forward, let's discuss about drugs first. Drugs are molecules of low molecular masses which interacts with their macromolecular targets to give biological response, these macromolecules can be carbohydrates, lipids, proteins and nucleic acids. When therapeutic responses are obtained then these drugs are known as medicines, while when they are taken in doses above than the prescribed one then they act as potential poisons. Drug designing is an inventive method of designing a molecule

ISBN : 978-93-91535-30-8

similar to the biomolecule which needs to be targeted, in shape and charge, allowing it to bind with its target to give out the biological responses by either activating or inhibiting the targeted molecule. Peptide-nanoparticle conjugates have become as a versatile tool for biomedical applications and are widely being used in drug designing and delivery system. Peptides are chain of amino acid sequences joined by covalent bond through a substitute amide linkage, this bond is known as peptide bond. Peptides contain only one free alpha amino group and one free alpha carboxyl group at the two opposite ends of a chain. Peptides are of various pharmacological uses as they can be easily synthesized chemically, have broad range of targets, low toxicity, high chemical and biological diversity, high potency and selectivity, good efficacy, safety and tolerability and low accumulation in tissues. Peptide as therapeutic drug is used as it allows increased stability towards proteolytic digestion and greater cell membrane permeability. Current strategies for the discovery of artificial bioactive peptides can be broadly divided into two categories: (i) the construction and screening of peptide libraries from random amino acid compositions within a certain macromolecular topology and (ii) the isolation of bioactive sequences from natural proteins based on their three-dimensional (3-D) structures.

Around 28 noninsulin peptide drugs have been approved worldwide and over 150 peptide drugs are in clinical development. Most peptides show some major drawbacks due to which their functions have been limit, these drawbacks are as follows: (i) lower target binding affinity and selectivity as compared to proteins. (ii) vulnerability to protease digestion in biological environments. (iii) short half-life due to which it requires frequent administration to maintain its efficiency. (iv) inability to maintain innate folding structures when isolated from proteins. While, it has been found that when these peptides are incorporated with non-biological elements, then these elements help to address major drawbacks of peptides.

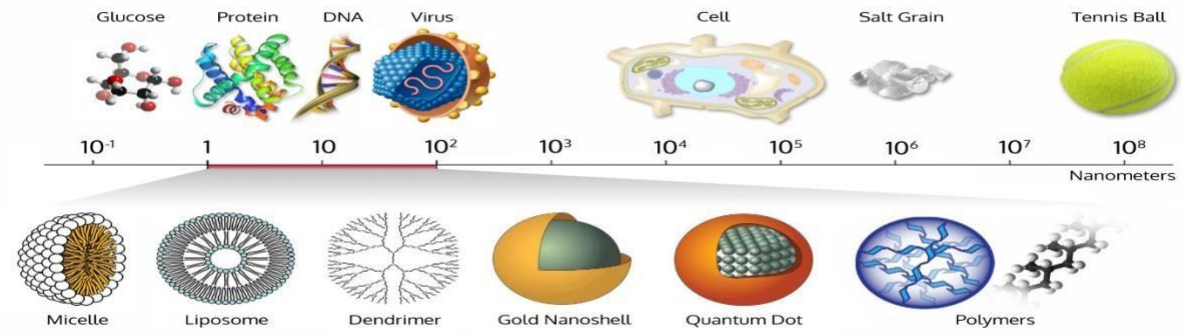

Fig.: comparison of bio-nanoparticles.

Source:https://www.wichlab.com/nanometer-scale-comparison-nanoparticle-size-comparison-nanotechnology-chart-ruler-2

Nanoparticles have the potential to serve as conjugate. They have the ability to improve the functionality of peptides and also act as abiotic component of peptides. Therefore, peptide nanoparticles conjugates have been taken under consideration for a variety of biomedical uses. In this

ISBN : 978-93-91535-30-8

review we are going to discuss about the advantages of using these peptide-nanoparticle conjugate system and their applications in biomedical areas along with some of the challenges that might come during clinical translation.

What is Peptide-Nanoparticle conjugation?

When a peptide molecule is combined with a nanoparticle in order to be used for biomedical applications is known as Peptide-Nanoparticle conjugation. Nanoparticles are of ultra-small size and have high surface-area-to-volume ratio which are beneficial to be engineered materials that can interact with other micro or nano biomolecules. Nanoparticles for the purpose of drug delivery are defined as submicron (less than 1 micro meter). These conjugations are helpful in reaching the sites of targeted biomolecules which other macromolecules fail to reach, with a lot more efficiency than the former one. Self-assembly of peptides helps in attaining the nanostructures. Peptides are able to gather into assorted nanostructures, including nanotubes, nanofibers, nanospheres and nanovesicles. Different types of peptides like cyclic and linear peptides, amphiphilic peptides, and alpha-helical and beta-sheet peptides have the ability to self-assemble themselves into nanostructures.

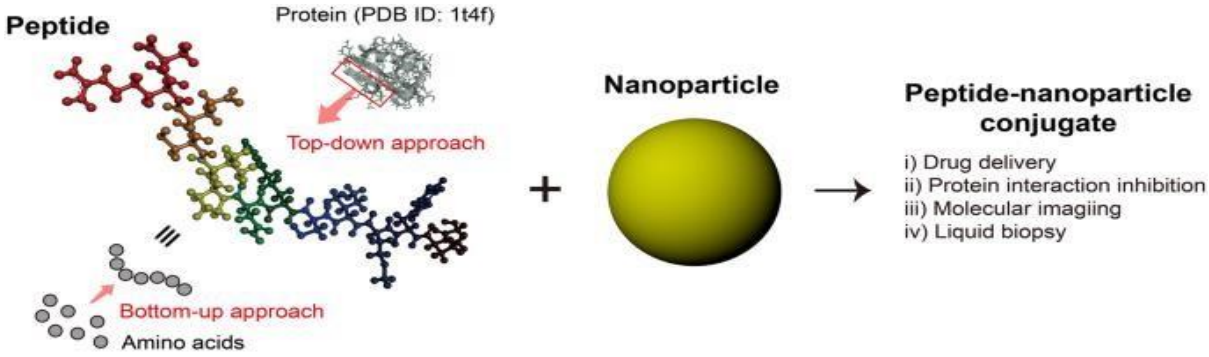

Fig.: Peptide-nanoparticle conjugation.

Source: https://nanoconvergencejournal.springeropen.com

Nanoparticles are made from biocompatible and biodegradable materials such as polymers, either natural like gelatin, albumin or synthetic like polylactides, polyalkylcyanoacrylates, or solid phase. Peptide-nanoparticle conjugation helps in enhancing the properties of nanostructures by providing the extra stability to the nanostructures.

Another property of using peptide-nanoparticle conjugate for biomedical applications is multivalency. Since, individual interactions of biomolecules in a biological system are weak non-covalent type of interactions like hydrogen bonding, ionic bonding, van der Waals forces, pie-pie stacking bonds, and hydrophobic interactions, therefore, this type of multivalent cooperative binding allows strong binding kinetics. These multivalent interactions of nanoparticles help in improved selectivity of biomolecules by using density of interaction of molecules on a surface to recognize the targeted molecule. Providing multiple binding sites to the peptides by these nanoparticles increase the opportunities of

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binding more binding partners. Many re-binding sites comes out during the process of dissociation, this can increase the time of retention of target materials on the surface. Also, the conjugation of different peptides gives additional functions of the hybrid materials, like immune response evasion, stimulus-responsive property and multi-target directed treatment with a single material. Nanoparticles have been utilized in in vivo imaging due to their ability to absorb and emit near infrared light of 700-1100nm and therefore, have the ability to give deep imaging and high spatial resolution. These absorbed light energy can be converted into heat and sound energy using photothermal and photoacoustic effects of nanoparticles and are beneficial in providing non-invasive treatment for diseases like cancer. Magnetic nanoparticles also, provides the treatment of remote diseases by selective accumulation at a target site in biological systems and release the molecules in a dose-controlled fashion. Magnetic nanoparticles are able to discriminate between the target biomolecules from a mixture of solutions very efficiently.

Important technological advantages of using peptide-nanoparticle conjugate system are: high stability; high carrier capacity; feasibility of incorporation of both hydrophilic and hydrophobic substances; feasibility of variable routes of administration, including oral administration and inhalation.

Application

(a)Targeted delivery of drugs :-

Peptide nanoparticles are very beneficial for pharmacologists to overcome the major challenge of delivery of drugs to the target sites in the body. Traditional small molecule drugs often suffers many pharmaceutical delivery obstacles such as non-specific delivery and inadequate accumulation at the sites. Peptides provide modular selectivity to drug delivery systems in many of the serious health problems like cancer and brain diseases. Peptides combined with nanoparticles is used for selectively deliver the drugs to the targeted tissues, these nanoparticles have the capability in encapsulate and protect therapeutic agents and increase the plasma circulation time of drugs.

One of the target delivery application of drugs include delivery to the nucleus of cell. Delivery of drug to the nucleus of cell is difficult as it contains many barriers. When a foreign particle enters the cell, it undergoes encapsulation and gets encapsulated in large vesicles then these vesicles move towards the lysosome and get degraded, also for entry of particles into the nucleus the particles need to be 20 to 150 nm in size in order to pass through the nuclear pore. Hence, these peptide-nanoparticles conjugation is a great way to overcome these two problems, as these are smaller in size and also acts upon the nuclear localization signal, received from nucleus.

One of the applications of nanoparticle conjugations is treatment of melanoma by transdermal delivery using peptide-nanoparticle conjugations. Existing techniques to overcome these skin barriers

ISBN : 978-93-91535-30-8

for topical delivery of bio-macromolecules, like plasmid DNA and protein rely on sophisticated mechanical devices, such as the ultrasonic apparatus, iontophoresis, microneedles and electroporation. Recently, the use of nanoparticles holds great deal in biomedicine for treatment of diseases. Receptor-targeting peptides are extensively used due to their improved binding specificity and effective accumulation of drugs at targeted sites. The main barrier which needs to be overcome during the treatment of melanoma is the outer most layer of skin i.e., stratum corneum. Compared to other bulk materials, nanostructures possess ultra-small size allows the drug to pass this barrier and reach the targeted site. According to an experiment performed by Niu et al., Au-nanoparticles based system was designed which employed conjugated TAT peptides for delivery of plasmid DNA, their results confirmed that TAT peptides boost skin infiltration and gene transfection of nanoparticles for an effective topological drug delivery system. A novel strategy for the treatment of cutaneous melanoma therapy involves topical delivery of a pDNA encoded with miRNA-221 inhibitor gene through HIV-1 twin-arginine translocation peptide (TAT) conjugated cationic gold particles (AuPT).Peptides along with nanoparticles have also been found to be useful to cross the other physiological barriers, including the blood brain barrier (BBB) that represents a major hurdle for effective delivery of pharmaceutical agents to the brain.

The peptide-nanoparticle conjugate-based approaches have demonstrated a number of successful examples that have achieved efficient targeting to diseased cells and permeation across physiological barriers.

(b)Drug delivery In chemotherapy of Tuberculosis:-

Tuberculosis requires frequent multiple-drug dosing. Introduction of drug in long-drug duration formulations releasing antimicrobial agents in slow and sustained manner could improve the adherence to the treatment and also the outcome of the treatment, which will in return allow reduction in frequency and number of doses. Drug carriers like nanoparticles serve as the medium to achieve the desired outcome.

Today, versatility to engineer the nanoparticles allows to deliver the drug in target-consideration manner, in desired pharmacokinetic profile, and considering route of administration of drug. In oral administration of nanoparticles-based drugs of TB, the uptake of particles occurs as follows: (1) by transcytosis via M cells, (2) by intracellular uptake and transport via the epithelial cells lining the intestinal mucosa, (3) by uptake via Peyer's patches.

It has been demonstrated that the nanoparticles provide sustained release of the anti-TB drugs with considerably enhanced efficacy after oral administration of drugs. Three drugs, rifampin (RMP), isoniazid (INH), and pyrazinamide were co-encapsulated in poly(lactide-co-glycolide) (PLG) nanoparticles were used. After single oral administration of drug in mice, it was observed that drug

ISBN : 978-93-91535-30-8

the drug could be detected in the circulation for 4 days (RMP) and 9days (INH and PZA); therapeutic concentrations were maintained for 9 to 11 days. In contrast, free drug remained in plasma only for 12 to 24 hours after administration. Treatment of infected mice with the nanoparticle-und drugs with five oral doses every 10th day resulted in complete bacterial clearance from the organs. While, free drugs were able to produce bacterial clearance only after daily administration of 46 doses.

Adhesion of nanoparticles with the mucosa enhances the absorption and of the associated drugs, thus increasing its bioavailability.

In inhaled administration of TB drug, higher drug concentration at the main site of infection and possibility of reduced toxicity is achieved. The pharmacokinetics and antibacterial effect of the nanoparticle-bound anti-TB drugs administered via respiratory route was investigated in guinea pigs. Sustained therapeutic drug levels for 6 to 8 days and in lungs for 11 days was achieved with single nebulization of RMP, INH, and PZA co-encapsulated in PLG nanoparticles to guinea pigs.

(c)Molecular imaging:-

Molecular imaging is a field of medical imaging that focuses on imaging molecules of medical interest withing living patients. It is a noninvasive way of characterizing and quantifying biological processes at cellular, tissue, and organism levels in intact living organisms. Nanotechnology has accelerated molecular imaging by enhancing the targeting efficiency of imaging probes.

Peptides have been employed successfully to achieve this purpose due to their long-term stability, target specificity, and rapid clearance from blood stream. Despite their advantages, peptides often suffer from weak binding affinity, metabolic instability, and fast renal clearance due to their small size. Nanoparticles can be helpful to address this problem by conjugating them with peptides, which have been used to improve the pharmacokinetics of the targeting peptides. Enhanced target-tobackground signal is achieved by peptide-nanoparticle conjugation could be achieved by conjugation of multiple imaging probes onto a nanoparticle's surface or by an increased surface density of specific peptides. Peptide nanoparticle conjugation can be applied for multitarget-directed nanotherapeutics can be by conjugation of different types of peptides, along with therapeutic agents.

Peptide nanoparticle conjugations are used as imaging probes for different applications like, nearinfrared (NIR) fluorescence imaging, computed tomography (CT), positron emission tomography (PET), magnetic resonance imaging (MRI), and multi-modal imaging.

Conclusion:

In this review, concept of peptide-nanoparticle conjugation is studied along with its applications in various biomedical fields. Nanoparticles are conjugated with peptides and various other drugs to produce therapeutic effect. These nanoparticles are smaller in size, hence, can easily pass the barriers

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which other macro biomolecules fail to pass. Nanoparticles conjugated with peptides increase their efficiency with lesser side effects to act upon a particular disease. Drugs encapsulated in nanoparticles have longer circulation period in plasma, they also have increased bioavailability, lesser doses are required having higher efficiency. Peptide-nanoparticle conjugates being smaller in size are also used in molecular imaging, due to their greater penetration ability. Nanotubes, nanowires, nanofibrils, spherical vesicles, and organogels are just a few examples of the new peptide materials.

The future advancement on this particular subject will be of great help to treat the diseases in a noninvasive manner with higher rate of success. This noninvasive method is advantageous to detect the disease in more precise form.

Despite the potential, application of peptide-nanoparticle conjugation in biomedical fields is difficult to achieve due to the following reasons: (i) the behavior of peptide-nanoparticle in physiological conditions, like bloodstream and intracellular spaces, have not been fully understood. (ii) peptides even encapsulated with nanoparticles are prone to degrade with the enzymatic actions of different enzymes. (iii) the potential immunogenicity of engineered PNCs should be address, it is a common obstacle for in vivo and clinical application. (iv) biological functions of peptide are lost when nanoparticles are conjugated covalently.

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