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Exploring The Role Of Nanocrystals In Hiv Therapy

[1]Gaurav B. Choudhari, [2]Bhagyashri A. Borade, [3]Sachin J. Dighade

[1]Student, [2]Assistant Professor, [3]Principle

[1]Department of B. Pharmacy.

[1]Institute of Pharmacy and Research Badnera, Amaravati, India

Abstract: Nanocrystals have emerged as a transformative approach in HIV therapy, addressing key challenges in drug delivery and efficacy. These submicron particles enhance the solubility and bioavailability of poorly water-soluble antiretroviral drugs, improving therapeutic outcomes. Nanocrystals facilitate targeted delivery, ensuring sustained drug release and reducing dosing frequency, which can enhance patient adherence. Additionally, their ability to penetrate biological barriers, such as the blood-brain barrier, provides an advantage in eradicating latent HIV reservoirs. Recent studies demonstrate that nanocrystal formulations can minimize systemic toxicity and drug resistance by maintaining consistent drug levels in plasma and tissues. Their versatility allows for incorporation into oral, injectable, and topical formulations. Despite promising preclinical and clinical results, challenges such as large-scale production, stability, and regulatory considerations need to be addressed. This review highlights the potential of nanocrystals as a game-changing tool in HIV therapy, offering new avenues for improving treatment efficacy and quality of life for patients.

Index Terms **- Nanocrystals, HIV therapy, drug delivery, bioavailability, antiretroviral drugs, sustained release.**

I. INTRODUCTION

AIDS, caused by HIV, has been reported worldwide since 1981, with major consequences for health care, society, and the economy. The United Nations Program on HIV/AIDS (UNAIDS) estimates that approximately 38 million people will be living with HIV in 2019, Some of the diseases related to AIDS have been responsible for seven million deaths since the start of the epidemic period. This disease/AIDS is related to the decline in productivity of a country caused by the disease, which affects the state's economy, business, and family. People who are unable to work and need a lot of treatment due to infectious diseases such as AIDS; resulting low productivity, high healthcare costs, and low income for affected families. It also undermines the foundation of human and human capital formation through loss of income and death of bread winners. This is due to negativity. It causes poor economic conditions, reduced parental care and socialization, reduced life expectancy, and increased need for medical care. It is also important in terms of poverty and inequality because the majority of people living with or affected by HIV cannot be prevented, treated, or cared for. Some measures are being taken and this is still a challenge to the fight against HIV/AIDS. To date, other infectious diseases, food insecurity, and other global health and development issues and still a challenge that most countries face. This is an indication that a multifaceted strategy is necessary in dealing with AIDS right from the prevention and early detection, treatment, and management of the disease together with the social and economic ramifications of this disease. AIDS is a condition that is precipitated by two different lentiviruses namely HIV-1 and HIV-2 HIV-1 is more prevalent; it is present worldwide, HIV-2 is mainly in West African countries and has spread to Europe and India since it was discovered in 1986 and it infects1to2 million people.[1]

Definition

Drug nanocrystals are crystals with a size in the nanometer range, which means they are nanoparticles with a crystal-line character. There are discussions about the definition of a nanoparticle, which means the size of a particle to be classified as a nanoparticle, depending on the discipline, eg, in colloid chemistry particles are only considered as nanoparticles when they are in size below 100 nm or even below 20 nm. 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); microparticles therefore possess a size of 1–1000 μm. 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" (in contrast to "microsuspensions" or "macrosuspensions"). In general the dispersed particles need to be stabilized, such as by surfactants or polymeric stabilizers. Dispersion media can be water, aqueous solutions or nonaqueous media (eg, liquid polyethylene glycol [PEG], oils). Depending on the production technology, processing of Drug microcrystals to drug nanoparticles can lead to an either Crystalline or to an amorphous product, especially when applying precipitation. In the strictest sense, such an amorphous drug Nanoparticle should not be called nanocrystal. However, often One refers to "nanocrystals in the amorphous state".[2]

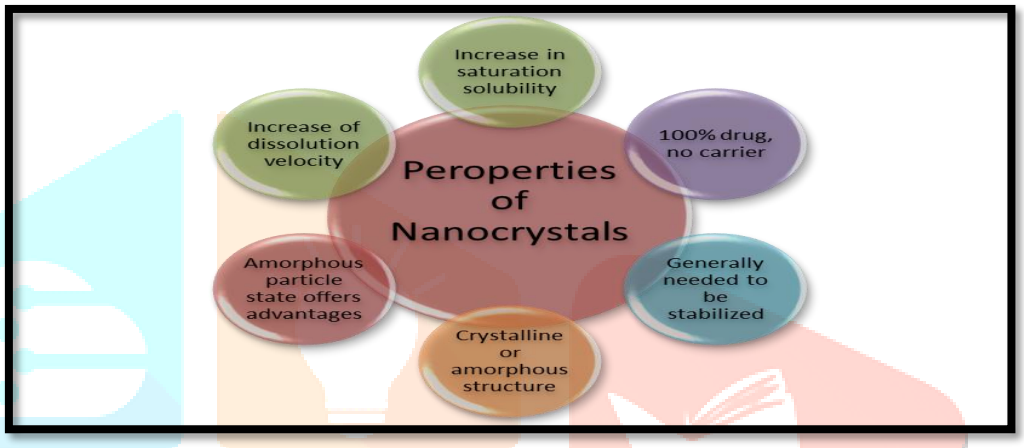


Figure no. 01: Peropertiers of Nanocrystals

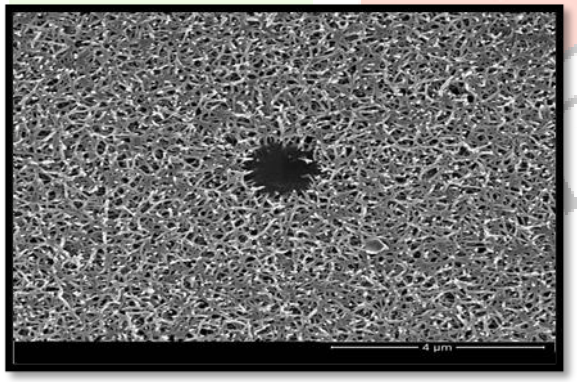


Figure no. 02 Electron microscopy picture of nanocrystals

Mechanisms of CD4+ T Cell Loss

This illness affects the immune response by progressively depleting the number of CD4+ T cells that are important in mediating immune response. This depletion results in severe immunosuppression, which puts a subject at risk of opening themselves up to opportunistic infections and other related effects. First, most of the patients have a mononucleosis-like illness and temporary reduction of their CD4 T lymphocytes after HIV-1infection. Afterward, there is a relative rise back to an early normal density of CD4+T cells is observed briefly. However, the repeated replication of the virus leads to a general activation of the immunity system and gradual, constant depletion of CD4+ T cells. CD4+T cells are not lost continuously; however, they are lost proportional to some parameters, including the viral load. Consider a patient who relapses back to AIDS in less time than those with low levels of viral load. This virus preferentially infect sand destroys CD4+T lymphocytes through direct cytolysis or immunologically induced apoptosis. For a while the thymus attempts to restore the number of T cells; when CD4+ counts plunge. The process of thymic renewal is no longer efficient. The process of thymic renewals is no longer efficient. The latency between initial contact with HIV viruses and the development of AIDS also varies, depending on the host as well as the virus's activity. Markers such as viral

load at a set point are very relevant in this regard. Reducing viral replication and increasing immune function is a general concept with the use of ART; however, immune function, CD4+T cell count, and immune dysfunction may never reach base line in some patients. Understanding these mechanisms is essential to develop strategies for the enhancement of CD4+T cell recovery for those with HIV and enhancing their quality of life.[3]

Antiretroviral Therapy (ART)

In the viruses' characteristics, both viruses are a like in the placement of one gene, the manner they reproduce, and how they spread about. However, significant differences exist: It is worth comparing both: HIV-2 is less contagious than HIV-1 and, in addition, its trans formation into AIDS takes more time. For instance, the chances of passing the HIV-2 from mother to child are at 5 percent while for HIV-1, the chances are between 20 to 25 percent.HIV-2 and HIV-1 share only 55 % sequence homology in their genome, and as such, management, treatment, and control differ; HIV-2 is less sensitive to some of the antiretroviral drugs used to treat HIV-1. HIV-2 is clinically defined by a stronger immune system response and as such, most of the patients are long-term non-progressors. This is important in the diagnosis and management of the two types hence the reason we need to know more about them.HAART came in 1996 as a revolutionary form of treatment for HIV/AIDS, where by the patient takes at least three antiretroviral drugs. With multiple prescribed drugs, the viral load in the patients is greatly lowered, enhancing the immune system, and increasing lifespan. HAART has changed HIV from a terminal illness to a chronic disease, and many patients can expect to live into their old age. The therapy not only reduces the AIDS morbidity and mortality but also halts the spread of the virus in the couple. Currently, HAART is considered standard, and progressive changes enhance the effectiveness of drugs as well as patient compliance.Among the therapies used in HIV is antiretroviral therapy which is mainly used to prevent the replication of the virus. ART comprises six classes of drugs, each targeting specific stages of the HIV lifecycle: ART is made up of six classes of drugs all of which operate at different stages of the HIV lifecycle.[4]

• Entry Inhibitors: These help to stop HIV from binding into as well as entering into the CD4 cells.

• NRTIs and NNRTIs: Nucleoside and non-nucleoside reverse transcriptase inhibitors are such that they inhibit the functioning of the enzyme reverse transcriptase by not permitting the transformation of viral RNA into viral DNA.

• Integrase Inhibitors: These inactivate integrase thus they cannot permit integration of viral DNA in the host cell's genome.

• Protease Inhibitors: They interact with the protease enzyme hence inhibiting the cleavage of the viral protein that is vital in the formation of new viruses.

• Fusion Inhibitors: These assist in the prevention of HIV interaction with the host's cell membrane.

• CCR5 Antagonists: This is because it binds it self to the CCR5 co-receptor located on the CD4 cells thus preventing the HIV from penetrating the cells.[5]

These stages are made possible through ART which leads to reduction in viral load and capacity of the immune system t of unction optimally thus improving the life span and quality of life of people living with HIV.The ideal vaccine against HIV-1 should mobilize both humoral and cellular immunity to afford protection against the virus. The neutralizing antibodies can inhibit HIV-1from entering cells initially. CD8+ T cells can then kill the infected cells and stop the development of a latent viral reservoir. Earlier clinical research has demonstrated that HIV-1-specific CD8+T cells correlate with the control of the viral infection during the acute phase. Subsequently, it has been shown that DCs and CD4+ T cells are also required for optimum HIV-1 specific immune responses. Recently, the use of nanoparticle platforms has been expanding for nanomedicine to elicit a specific immune response for prophylactic and therapeutic vaccination against HIV.[6]

Antibody Activation and T Cell Responses

Animal model studies have shown that nanocrystal containing HIV vaccines can stimulate activation of good quality antibodies which are neutralizing and long acting capable of protecting the body against most HIV strains. These vaccines also recognize strong HIV specific cd4 and cd8 T cell responses that may be crucial in suppression of viral replication and clearance of infected cells. Future studies will continue to refine the characteristics of nanocrystals and their matrix to enhance immuno adjuvanticity and apply the discovered preclinical effectiveness of nanocrystalline adjuvants to HIV vaccine development for clinical practice.[7]

Long-Acting Drug Delivery Technologies

There is also considerable validation that use of antiretroviral remedy, or ART, can greatly reduce the trouble of sexual transmission of HIV if the viral weight is sufficiently low. Nucleoside/nucleotide hinder transcriptase impediments (NRTIs) are active factors of ART rules that are planned for viral weight reduction. Two of these NRTIs, constantly used in the se combinations are lamivudine(3TC) and zidovudine(AZT). NRTIs help the hinder transcriptase enzyme that HIV requires when transcribing viral RNA into DNA that is suitable to integrate into the host cell; 3TC and AZT are nucleoside analogues of cytidine and thymidine singly. Integrate din to the viral DNA chain by hinder transcriptase, they lead to the truncation of the DNA chain which can't replicate incase of HIV. When taken with other specified specifics, ART rules containing 3TC and AZT or other NRTIs suppress their HIV viral loads to below 200 duplicates/ mL, which is considered undetectable. An "undetectable viral weight" is a point where the trouble of infecting a sexual mate can't be done. In the HPTN052 study where early induction of ART was specified the trouble of transmission of HIV from the infected to the uninfected mate was reduced by a stunning 93 compared to the situation if ART was initiated late. Consequently, drugs like 3TC and AZT that are used in ART when taken according to the croaker's recommendation they help in managing HIV viral weight and reduce the chances of transmitting the contagion during sexual intercourse. The most effective way to avoid HIV is to make sure that viral count isn't sensible. Structural Modification of APIs: It is well understood that modifications of the hydrophilicity of APIs affect their absorption and bioavailability.[8,9,10]

Key advantages of Nanocrystals in HIV Therapy

Enhanced Bioavailability

One of the primary benefits of nanocrystals is their ability to significantly increase the bioavailability of antiretroviral drugs compared to traditional formulations. This improvement is crucial, as higher bioavailability ensures that more of the active drug reaches systemic circulation, thereby enhancing therapeutic effects and potentially reducing the required dosage. For instance, studies have demonstrated that nanocrystallized formulations can maintain effective drug concentrations in the body for extended periods, which is vital for managing chronic infections like HIV-3.

Sustained Release

Nanocrystals facilitate controlled and sustained release of medications, which is essential for maintaining stable drug levels over time. This prolonged release can lead to improved adherence to treatment regimens, as patients may need fewer doses compared to conventional therapies. Research has shown that nanocrystal formulations can keep drugs in circulation at therapeutic concentrations for longer durations, thus minimizing the peaks and troughs associated with standard dosing schedules.

Targeted Delivery

Another significant advantage of nanocrystals is their ability to be engineered for targeted delivery. This capability allows for precise targeting of specific tissues, such as lymphoid reservoirs where HIV persists. By focusing on these areas, nanocrystals can enhance the effectiveness of treatment against latent infections, potentially leading to better outcomes in eradicating the virus from reservoirs. This targeted approach not only improves drug efficacy but also reduces side effects by minimizing exposure to non-target tissues.[11,12]

Production of nanocrystals

Bottom up technology

Precipitation methods

The drug is dissolved in a solvent and subsequently added to a nonsolvent, Leading to the precipitation of finely dispersed drug nano Crystals. One needs to bear in mind that these nanocrystals Need to be stabilized in order not to grow to the micrometer Range. In addition, the drug needs to be soluble in at least one Solvent, which creates problems for newly developed drugs That are insoluble in both aqueous and organic media. These Are some reasons why, to our knowledge, this technology has Not been applied to a product as yet. Another precipitation method is the preparation of Amorphous drug nanoparticles, for example, as carotene Nanoparticles in the food industry. A solution of the Carotenoid, together with a surfactant in a digestible oil, are Mixed with an appropriate solvent at a specific temperature. To obtain the solution a protective colloid is added. This Leads to an O/W two phase system. The carotenoid stabilized By the colloid localizes in the oily phase. After lyophilization X-ray analyzes shows that approximately 90% of the Carotenoid is in an amorphous state.[13,14]

Top down technology

Milling methods

The classical Nanocvrystals technology uses a bead or a pearl mill to achieve particle size diminution. Ball mills are already known from the first half of the 20th century for the production of ultra fi ne suspensions. Milling media, dispersion medium (generally water), stabilizer and the drug are charged into the milling chamber. Shear forces of impact, generated by the movement of the milling media, lead to particle size reduction. In contrast to high pressure homogenization, it is a low energy milling technique. Smaller or larger milling pearls are used as milling media. The pearls or balls consist of ceramics (cerium or yttrium stabilized zirconium dioxide), stainless steel, glass or highly crosslinked polystyrene resin-coated beads. Erosion from the milling material during the milling process is a common problem of this technology. To reduce the amount of impurities caused by erosion of the milling media, the milling beads are coated. Another problem is the adherence of product to the inner surface area of the mill (consisting mainly of the surface of the milling pearls and the surface of the mill itself). The milling time depends on many factors such as the surfactant con-tent, hardness of the drug, viscosity, temperature, energy input, size of the milling media. The milling time can last from about 30 minutes to hours or several days. This technology is an important particle size reduction technology which is proven by four FDA-approved drugs using it, which will the subject later in this text.[15]

Homogenization methods

When producing nanocrystals using homogenization methods, There are three important technologies namely: Microfluidizer Technology (IDD-P™™ technology), Piston gap homogenization in water (Dissocubes technology) and in water mixtures Or in nonaqueous media (Nanopure technology).The Microfluidizer technology can generate small Particles by a frontal collision of two fluid streams under Pressures up to 1700 bar. This Leads to particle collision, shear forces and also cavitation Forces. It can be achieved with jet stream Homogenizers such as the microfluidizer. The collision chamber can be designe in two shapes, being either Y-type or Z-type. Surfactants are required to stabilize the desired particle size. Unfortunately ,a relatively high number of cycles (50 to 100 passes) are necessary for a sufficient particle size reduction. SkyePharma Canada Inc. (formerly RTP Inc.) uses this principle for their Insoluble Drug Delivery – Particles (IDD-P™) technology to achieve the production of submicron particles of poorly soluble drugs.[16,17]

Targeted drug delivery Of antiretrovirals

Targeted delivery of antiretrovirals to HIV-1-infected T-cells And macrophages would improve the efficacy of antiviral Drugs, reduce toxicity, reduce HIV-resistance frequency, And decrease viral production. However, the specificity Of intracellular delivery and transport is related to many Factors including the type and number of targeting ligands Required for optimal cellular uptake. Various mechanisms Of intracellular delivery of the antiretroviral drug include Passive diffusion of free drug, nonspecific phagocytosis of a Nanocarrier, pinocytosis and receptor-mediated endocytosis. Another advantage of nanocarriers includes its ability to Bypass the multidrug-resistant transporters, which may efflux Drugs entering freely through the plasma membrane. Inorganic solid lipid nanoparticles liposomes, polymeric Micelles, dendrimers, cyclodextrins, and cell-based Nanoformulations have been studied for delivery of drugs Intended for HIV prevention or therapy.43 For anti-HIV drugs to Be effective, adequate distribution to specific sites in the body Must be achieved, and effective drug concentrations must be Maintained at those sites for the required period of time. For Effective delivery of anti HIV-1 nanotherapy, an optimal drug-Delivery nanocarrier vehicle must be generated that should be Of a precise geometry, whose surface (ie, zeta potential, stealth Ligands), drug/biomolecule (antiretrovirals, oligonucleotides, Proteins, small interfering RNA [siRNA], RNA, imaging agents) Encapsulation efficiency and release, surface chemistries (targeting Antibodies, PEG chains, metal chelators), and spatial distribution Of ligands must be well engineered. Targeted nanocarrier delivery Involves (1) the recognition of HIV-infectable target cells and Tissues; (2) the ability to reach these sites; and (3) the ability to Deliver multiple therapeutic agents. Macrophages have been used as cellular transporters for Antiretroviral nanoparticles or nanoformulated antiretroviral Drugs (nano-ART) distribution and that the efficacy of Antiretroviral medications can be significantly improved By repackaging them into nanoparticles.[18]

Nonviral Carriers For Exogenous siRNA Delivery For HIV Therapy

Delivery methods using nonviral carriers employ synthetic and/Or natural compounds to deliver nucleic acids such as siRNA orDNA into cells. Compared to viral vectors, nonviral nucleic acid carriers exhibit considerably reduced transfection efficiencies and nonviral methods are generally considered to be less effective than viral methods. However, unlike viral methods, the materials used in the fabrication of these carriers are less toxic and less immunogenic compared to viral vectors. Other advantages of nonviral carriers include

biocompatibility, the potential for targeting or site-specific drug delivery, the ease of production of these carriers, especially in laboratory-scale formulations, and the potential for repeat administration without stimulating the immune system. Nanotechnological nonviral approaches for exogenous siRNA delivery for HIV/AIDS include the use of liposomes, polymeric nanoparticles, dendrimers, quantum rods, carbon nanotubes, and inorganic nanoparticles. The ideal delivery system must bind or encapsulate the siRNA in a reversible manner to facilitate siRNA delivery and release to the cell cytoplasm, protect the siRNA from degradation in circulation and in endosomes, be biocompatible and biodegradable, and also prevent clearance by the liver and kidney. Discussed below are the various carrier-based, nonviral approaches described in the literature for the delivery of exogenous, therapeutic anti-HIV siRNA for HIV treatment.[19]

Liposomes. Liposomes are self-assembled nano- or micro-Particles or colloidal carriers that spontaneously form when Certain lipids are hydrated in aqueous media. They consist Of an aqueous volume enclosed by a membrane of one or more Bilayers of natural and/or synthetic lipids (Figure No 05). Drugs May be encapsulated in the aqueous core or intercalated in the Bilayer via passive mechanisms (i.e., drug encapsulation occurs During liposome formation) or actively (i.e., after liposome Formation).

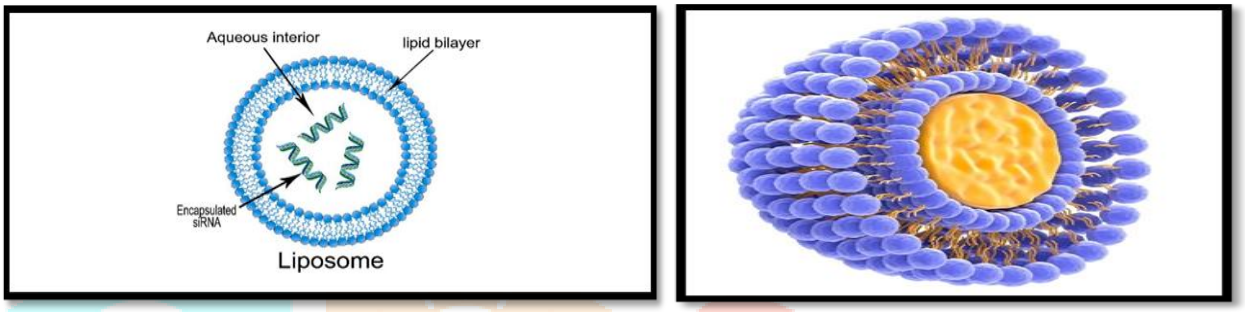


Figure No.05: Liposomes

Liposomes may be classified based on their size and number Of bilayers into two categories, namely, multilamellar vesicles (MLV) (concentric phospholipid spheres separated by layers of Water) and unilamellar vesicles (a single spherical phospholipid Bilayer enclosing an aqueous core). The unilamellar vesicles Can be further classified into large unilamellar vesicles (LUV)And small unilamellar vesicles (SUV). The structure formed is important because the liposome size and the number of bilayers impact the circulation half-life and the drug loading, respectively. The main constituent of conventional liposomes is phospholipids, which are also the main components of the cell membrane; thus, phospholipids and liposomes have excellent biocompatibility.[20]

Polymeric Nanoparticles. Polymeric nanoparticles (Figure No 07) are defined as sub-micron-sized colloidal systems (1−1000 Nm) that can be fabricated from a variety of natural or synthetic Polymers (biodegradable or nonbiodegradable) in various Compositions. Polymeric nanoparticles can be broadly Classified into two categories based on their method of Preparation: nanocapsules, which are reservoir or vesicular Systems in which a liquid or semisolid drug-loaded core is surrounded by a polymeric membrane, or nanospheres, which Are matrix systems in which the drug is uniformly dispersed Throughout a solid polymer matrix. Depending on the Method of preparation, the drug may be entrapped, dissolved, Dispersed, encapsulated, or attached to the nanoparticle Matrix.[21]

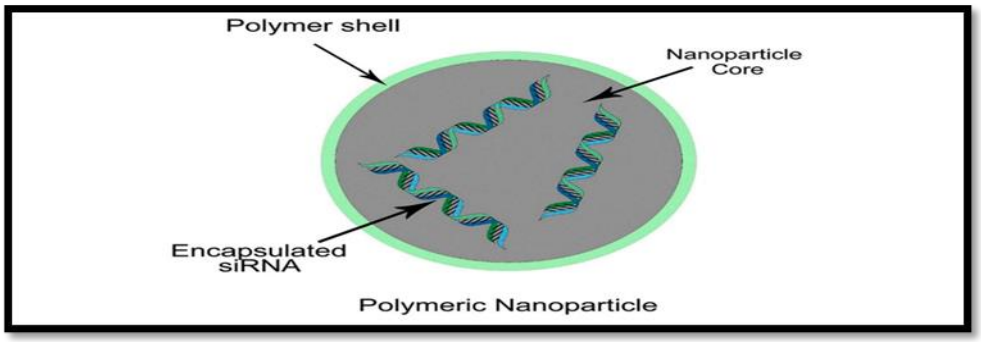
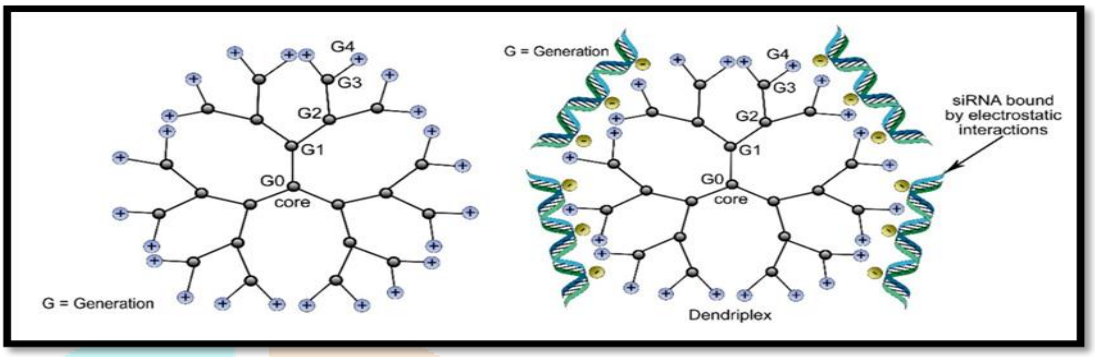


Figure No. 07: Polymereric Nanopaerticle

Polymers used in the fabrication of nanoparticles can be Broadly classified into biodegradable and nonbiodegrad-Able. The ideal polymer for use in the preparation of Nanoparticles must be biodegradable and must be completely Eliminated from the body in a short time such that uncontrolled Accumulation leading to lysosome and cellular overloading isAvoided, allowing it to be repeatedly administered safely.[22]

Dendrimers. Dendrimers are monodisperse, polybranched, usually highly symmetrical synthetic three-dimensional polymers in the nano range (Figure No 08). Dendrimers have well-defined chemical structures that can be differentiated into three parts, comprising an initiator or central core, interior layers, also referred to as generations (which are branches radiating from the core and made up of repeating units), and the exterior part that terminates the outermost interior generation and plays an important role in complexation of nucleic acids or dendrimer drug carrying ability.Dendrimer synthesis has generally been carried out using two main strategies; however, other approaches have been reported. The first is described as the divergent approach. In this method, the growth of dendrimers (or increase in generations) originates from a core site, whereas in the second method, referred to as the convergent approach, several dendrons are reacted with a multifunctional core to obtain a dendrimer product. The most widely used dendrimers in biomedicine and drug delivery (PAMAM and polypropylenimine (PPI) dendrimers) are synthesized using the divergent method.[23,24]



Figurer no. 08 Dendrimers

Inorganic Nanoparticles and Carbon Nanotubes.

Inorganic nanoparticles have been successfully used for delivery of nucleic acids. Some of the inorganic materials used for this purpose that have been reported include carbon nanotubes, quantum dots, gold, and silica, to mention a few. Inorganic nanoparticles have been reported to have moderate transfection efficiencies; however, their non susceptibility to microbial attack, ease of preparation, and good storage stability are some of their advantages over organic nanoparticles. The advantages and disadvantages of inorganic nanoparticles that have been used to deliver siRNA for HIV therapy. [25]

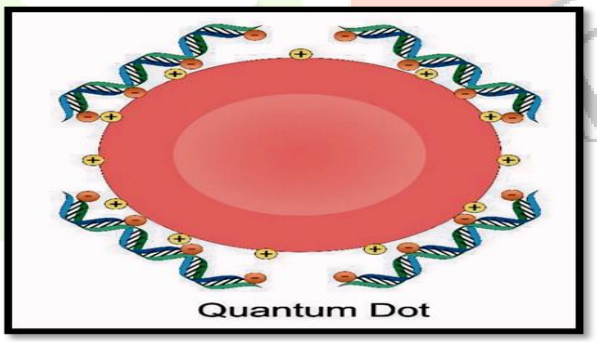


Figure no. 09 Quantum Dot

Anti-HIV-1 siRNA therapeutics

Recent advances in the field of nanotechnology offer an Unprecedented opportunity to enhance the power of siRNA- Mediated gene therapy by providing both an efficient delivery System as well as targeted specificity. siRNA-mediated Knockdown of gene-specific messenger RNA (mRNA) levels Is a great therapeutic strategy, in which double-stranded RNAs are cleaved by the cellular nuclease Dicer into short fragments referred to as siRNA, which enter A ribonuclease protein complex called the RNA-induced Silencing complex. This complex mediates a specific Degradation of the corresponding mRNA. Nanoparticles Can form stable complexes with siRNAs, called nanoplexes. A nanoplex is a generic term for a nanoparticle complexed to another biological component, which could be a drug, an siRNA, a imaging agent and antibody, a peptide, etc. siRNA technology is a novel method to achieve complete and persistent knockdown of gene expression.[26] Delivery is a key determinant as to whether or not RNA interference-based therapeutics will have clinical relevance and delivery encompasses extracellular transport of the nanoplex to target cells, its intracellular RNA trafficking, and processing. Gold nanoparticles are particularly attractive for therapeutic applications due to their

biocompatibility and ease of complex formation with biomolecules. Gold nanorods (GNR) have far-reaching potential for the study of intracellular processes at the single-molecule level, using high-resolution cellular imaging, long-term observation of cell trafficking in vivo, and gene silencing. The hydrodynamic size of these GNR-nanoplexes under physiological condition is ,100 nm, making them ideal as intracellular delivery agents. Gold nanoparticles have been used for more than a decade as a gene carrier for plasmid DNA and oligonucleotides, but recently our group was the first to report the use of GNR for the delivery of siRNA against dopamine- and cyclic-adenosine monophosphate-regulated phosphoprotein of molecular weight 32,000 (DARPP-32) in vitro.90 Figure 3 represents a schematic of the cationically charged PEGylated GNRs electrostatically coupled with negatively charged siRNA to form stable nanoplexes. We evaluated these nanoparticles as nonviral gene carriers by investigating their specificity and efficiency in achieving DARPP-32 gene silencing in primary dopaminergic neuronal cells, which are typically difficult to transfect. These nanoplexes were also found to transmigrate across an in vitro model of the BBB without compromising the integrity of the barrier, while retaining their gene-silencing efficiency. These results have enormous implication in the treatment of drug addiction in HIV-1-infected drug-abusing patients. These observations have further underscored the tremendous benefits that nanotechnology can offer towards the safe and efficient delivery of siRNA-based therapeutics in the brain and other organs.[27]

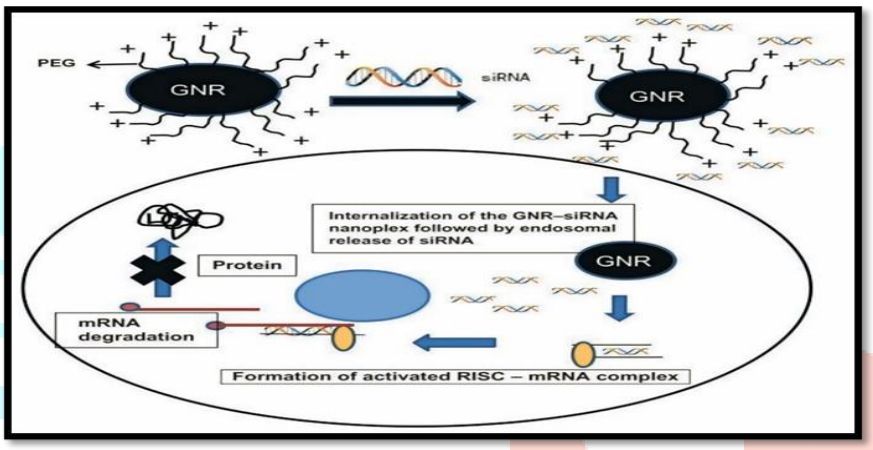


Figure no. 10 Schematic of cationically charged PEGylated GNRs electrostatically coupled with negatively charged siRNA to form stable nanoplexes.

To enhance the cellular uptake of siRNA molecules, Cell-penetrating peptides (CPP)-mediated siRNA delivery Employing a disulfide bond formation between peptide Transduction domain (PTD)/CPP and siRNA is typically Utilized. Some of the most well characterized CPPs are TAT peptide, penetratin, transportan, polyarginine and MPG. Recently, studies evaluated the in vivo efficacy Of structurally flexible, cationic PAMAM dendrimers as A siRNA-delivery system in a humanized mouse model For HIV-1 infection. They have also developed novel dual Inhibitory anti-glycoprotein-120 aptamer–siRNA chimera With potent anti-HIV activities and have further constructed A chimerical RNA nanoparticle that contains a HIV gp120-Binding aptamer escorted by the packaging RNA (pRNA) of Bacteriophage phi29 DNA-packaging motor. These pRNA–Aptamer chimeras specifically bind to and are internalized Into cells expressing HIV gp120 and inhibit HIV function By blocking viral infectivity. This nanoplex represents a Potential HIV-1 inhibitor, and provides a cell-type-specific siRNA-delivery vehicle, showing promise for systemic anti-HIV therapy. Our group demonstrated an almost 90% viral suppression using a nanoparticle (QR)-conjugated well validated siRNA (si510) that targets the poly-A/TAR (transactivator of the HIV-1 LTR) site and suppresses viral Replication in the THP-1 monocytic cells. Dendrimers have, As reflected by reduction of trans endothelial resistance Across an in vitro BBB on treatment with QR-conjugated Matrix metalloproteinase-9 (MMP-9)-siRNA due to Downregulating the expression of MMP-9 gene in brain Microvascular endothelial cells that constitute the BBB. Thus siRNA therapeutics for HIV infection have been Demonstrated in many studies, but limitations of this strategy Include successful strategies to deliver siRNA to the desired Target cells such as T cells, macrophages, dendritic cells, And tissues. Despite these limitations, siRNA therapeutics Possesses great potential in HIV therapy.[28]

Challenges and future Directions

Regulatory Hurdles: The approval process for nanomedicine products is notably complex, requiring extensive safety and efficacy data. This complexity can delay the introduction of innovative therapies into the market, hindering timely access for patients who could benefit from advanced treatments. Regulatory bodies often demand rigorous testing to ensure that these novel formulations do not pose unforeseen risks, which can be a lengthy process.[29]

Manufacturing Scalability: Another critical challenge is the scalability of manufacturing nanocrystal formulations while maintaining consistent quality. The production of nanoparticles must adhere to stringent quality control measures to ensure that each batch meets the required specifications. This is particularly challenging given the intricate nature of nanotechnology, where slight variations in size and surface properties can significantly affect the therapeutic efficacy and safety of the product

Long-term Effects: The long-term safety of nanoparticles in vivo remains a significant concern. Comprehensive studies are necessary to evaluate how these particles interact with biological systems over extended periods. Understanding their bio distribution, metabolism, and potential toxicity is crucial to ensuring patient safety Future research should prioritize optimizing nanoparticle formulations for various routes of administration, such as intravenous or subcutaneous delivery, which could enhance their therapeutic effectiveness. Additionally, assessing long-term safety profiles through rigorous preclinical and clinical trials will be essential in building confidence in these therapies among healthcare providers and patients alike. Conducting diverse clinical trials will also help evaluate the efficacy of these formulations across different patient populations, addressing the variability in individual responses to HIV treatment. By overcoming these challenges, nanocrystal-based therapies could revolutionize HIV treatment and potentially lead to improved patient outcomes.[30]

CONCLUSION

The current review explores the potential of nanocrystals in advancing HIV therapy, focusing on how nanotechnology can enhance the efficacy of antiretroviral treatments. Nanocrystals offer improved bioavailability, sustained drug release, and targeted delivery, which are crucial for optimizing HIV treatments. By increasing solubility and maintaining stable drug levels, these nanocrystals can help in overcoming the limitations of conventional therapies. The document also highlights the challenges in scaling production, regulatory hurdles, and the need for long-term safety studies. Even with these challenges, nanocrystal-based approaches represent a promising future for HIV therapy, potentially improving patient outcomes and reducing the burden of the disease.

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