Chapter

Nanotechnology Based Drug Delivery for HIV-AIDS Treatment

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Abstract

One of the biggest challenges of the world in this 21st century is to cure HIV-AIDS. In Present scenario different antiviral drugs are available in the market to reduce the worse condition and manage improved survival rate. These drugs are manageable but their bioavailability, lower permeability and poor half life of the drugs have limitations. If the drug is preferred in higher dosage in AIDS patients, the drug leads to toxicity and adverse effects to patients and increase resistant against HIV & if the drug is preferred in lower dose along with nano carriers it will reach the target area for beneficial effect, therefore drugs Lacking of Knowledge in Potent Drug delivery systems is due to instability, chemical degradation and tissue barrier difficulties are reasons to reach drug target successfully. In this scenario Nanotechnology based antiretroviral drugs delivery holds drug and will provide to cure AIDS. Nanotechnology based deliver system Nanocarriers like Liposomes, dendrimers, Nanoparticles, Polymeric Micelles, Nanovesicles, Nanoemulsion provide the way to deliver drug to targeting tissue. Nanobased carriers revolutionized the field of Pharmaceutics and Pharmaco Kinetic's in target drug delivery. The present study depicts nano based ARV drug provides increase efficiency with less adverse effects to control HIV. Like same way we can provide and increase nanobased drug delivery capacity to other available HIV drugs.

Keywords: HIV, AIDS, Antiretroviral Drugs, Nanocarriers, Nanotechnology, Drug delivery

1. Introduction

One of the most severe public health issues in the world is the Human Immunodeficiency Virus (HIV), the virus that causes Acquired Immunodeficiency Syndrome. HIV-AIDS remains one of the most difficult conditions to treat in the 21st century. However, multiple antiretroviral medications are present in the present situation, rendering the disease chronic rather than worse, which helps to improve the survival rate. According to the Statistical survey of WHO 2019 (World Health Organization), there are 38 million people living with HIV infection from that 1.7 million people newly added with HIV- infection in 2019 and 6.9 million people died from this 68% people accessed to Antiretroviral therapy [1]. In the late 20th century, it was reported that two strains of HIV diverge from SIV (Simian immunodeficiency Virus) from which HIV-1 spread across the world, and HIV-2 is more prominent in Africa [2]. HIV invades the mucosal membrane, destroys

the immune system, leaving a wide variety of bacteria, viruses, fungi, protozoa vulnerable to infection in the host body. By exchanging body fluids due to blood transfusion, organ transplantation, physical intercourse, from affected parent to offspring, HIV infection propagates. One of the key sources of entry through the mucosal surfaces is the sexual transmission. The primary path of heterosexual HIV transmission is the female genital tract [3]. Sexual transmission via the rectal route is also a major issue that, due to its physiology, renders it more vulnerable to HIV infection [4]. Immune cells, i.e. macrophages and dendritic cells found in the sub-epithelial layer of the vagina or cervix mucosa are the main targets of HIV infection [5] in **Figure 1**.

During copulation, it moves by semen or other biological fluids that penetrate the stratified squamous epithelium or vaginal columnar epithelium to invade the target cell. HIV has a glycoprotein called gp120 on the surface of the viral coat, which attaches to the T-helper lymphocyte transmembrane protein receptor CD4 or chemokine receptor CCR5, CXCR4, and infects the cell [6]. Through endocytosis, HIV infects the host cell and fuses with the host cell membrane and releases into the host cytoplasm, it undergoes reverse transcription by incorporating proviral DNA into the host genomes. It then releases new viral particles that come out of it to infect the other cells. It infects macrophages and depletes the quantity of CD4+ cells that are the distinctive characteristics of an infection with HIV [7]. The use of multiple genes by HIV viruses (a) Main genes: gag, pol, and env (b) regulatory genes: tat, rev, nef, vif, vpr, and vpu, boost the productivity and hijacking the host's cellular system and develops its offspring to infect other cells [8]. Viral particles linger in the key after active infection in anatomical location such as dendritic cells,

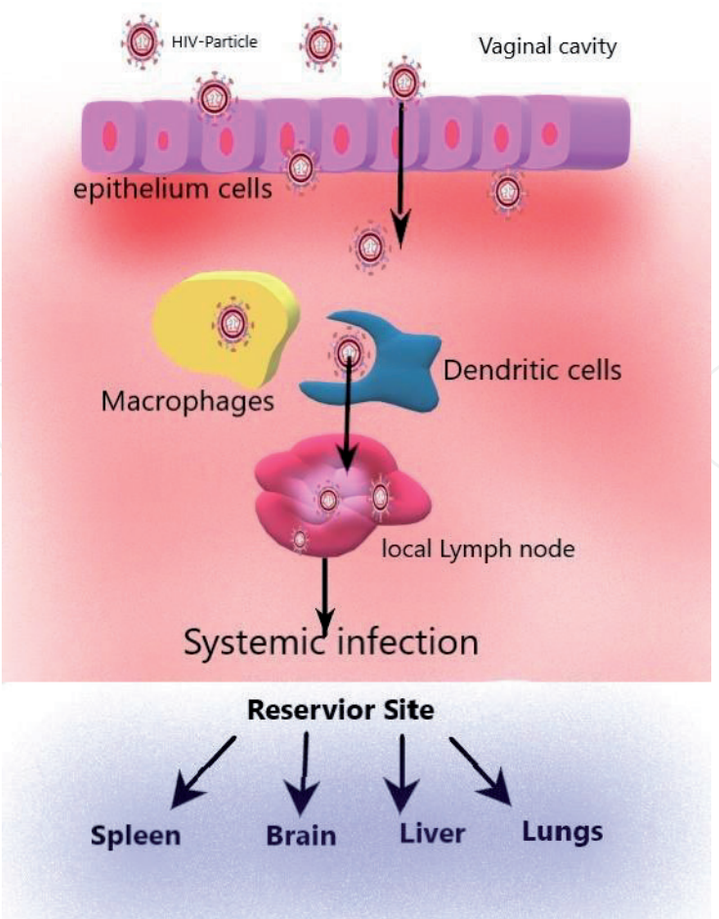

Figure 1.
Pictorial representation of HIV particle invasion.

macrophages, bone marrow, lymph nodes, spleen, lung, Central nervous system (astrocytes, microglial cells) [9–11]. When it remains in the CNS and induces a major loss in neural networks and eventually it leads to severe problems, such as HIV-associated dementia (HAD) If the patient is not, Well treated, it's going to die in 5–10 years (**Figure 2**) [12].

Various antiretroviral medications are used in the present scenario. Accessible in the market in a different mix, depends on the point of infection. High antiretroviral activity Therapy (HAART) is used to treat HIV/AIDS. It was introduced in 1996 and requires a mixture of at least three antiretroviral (ARV) medications. This treatment has been used to prolong the lifespan of HIV-infected patients [13]. However, this treatment is used to treat some of the infections Extension, but complete recovery has not yet been achieved as these ARV medications have certain drawbacks, such as mild water solubility, limited controlled release, low half-life reactivity, reduced blood barrier permeability, poor bioavailability is one of the major issues [14, 15]. ARV operates on the theory of blocking and inhibiting pathways, depending on the stage of the HIV cycle. Inhibitor of reverse transcriptase Blocks the action of the reverse transcriptase enzyme that prevents the conversion of viral RNA to DNA. Various nucleotide analogs drugs which incorporated in between the reverse Tran scripting chain in the host cytoplasm and terminate the process and non-nucleotide analogs drug bind to the reverse transcription enzyme and block the life cycle [16]. Various forms of AIDS treatment regimens are available that are available on the market. It has been prescribed. However, it is difficult to choose the right mixture of ARV products because of different considerations such as drug properties, drug tolerance status, patient reactivity, drug costing, drug toxicity, or some other adverse drug effect [17]. The biggest downside of the ARV treatment is the shorter period of availability in the bloodstream of the body in such a way that the viral particle at the location of reservoirs such as CNS, lymph nodes, and lungs

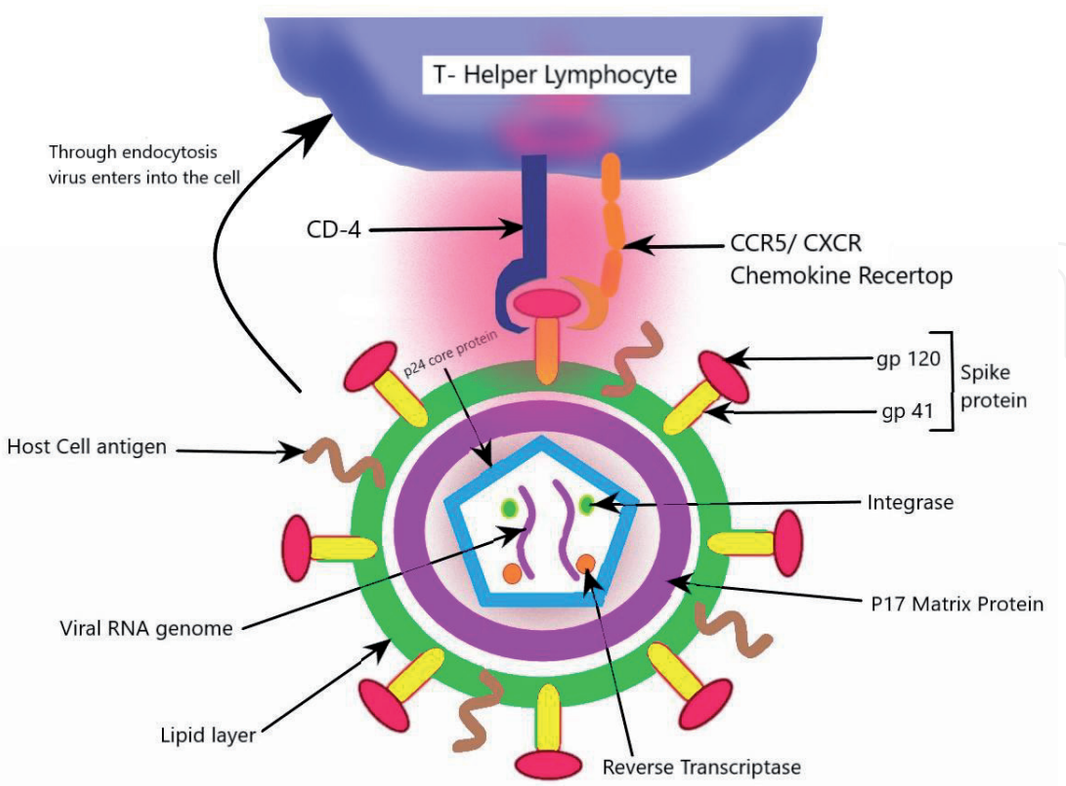

Figure 2.
Pictorial art representing ligand receptor/co-receptor interaction between the HIV virus and Cd4 cell.

is less exposed to the drug, such that higher doses of the viral particle are needed for a sustained period of time that develops resistance to the HIV strain [18]. The reservoir also includes latently infected cells, including CD4+ T-cells, Monocytes, macrophage lineage carrying incorporated transcription of the provirus silencing within the genome that might also re-infect the patient due to activation of the proviral genome [19]. In order to resolve such problems and drawbacks, nano-based drug delivery technologies, nano-medicines, and other nano-based strategies play a key role in drug effectiveness, drug reactivity, drug target accuracy, minimizing drug toxicity and negative impacts, and various major challenges currently facing ARV drugs in the present context.

2. Current anti-retro viral drug available in market for HIV-AIDS treatment

In present situation, HAART (Highly active anti-retroviral Therapy) regimen work on the principles by blocking replication process, reverse transcription, protein maturation process and viral-DNA integration process in to the host chromosomes. To inhibit this all process various class of drugs are available in the market which include Nucleotide reverse transcription inhibitors (NRTI), Non nucleotide reverse transcriptase inhibitors (NNTRI), integrase inhibitors, protease inhibitors as mention below in Error: Reference source not found (**Table 1**):

Non-nucleoside reverse transcriptase inhibitors (NNRTI)			
Generic names	**Abbreviations**	**Brand name**	**Manufacturer**
Efavirenz	EFV	Sustiva®	Bristol-Myers Squibb
Etravirine	TMC125	Intelence®	Tibotec
Nevirapine	NVP	Viramune®	Boehringer Ingelheim
Delavirdine	DLV	Rescriptor®	ViiV Health care.
Reverse transcriptase inhibitors (NRTI)			
Didanosine	ddI	Videx®	Bristol-Myers Squibb
Zalcitabine	ddC	HIVID®	Roche
Lamivudine	3TC	Epivir®	GlaxoSmithKline
Abacavir	ABC	Ziagen®	GlaxoSmithKline
Zidovudine	AZT	Retrovir ®	GlaxoSmithKline
Tenofovir	TDF	Vemlidy®	Gilead Sciences
Stavudine	d4T	Zerit®	Bristol-Myers Squibb
Integrase inhibitors			
Generic names	**Brand name**	**Manufacturer**	
Raltegravir	Isentress®	Merck	
Dolutegravir	Tivicay®	ViiV Health care.	
Protease inhibitors			
Generic names	**Abbreviations**	**Brand name**	**Manufacturer**
Saquinavir	SQV	Invirase®	Roche
Atazanavir	ATV	Reyataz®	Bristol-Myers Squibb
Indinavir	IDV	Crixivan®	Merck

Nelfinavir	NFV	Viracept®	Agouron Pharmaceuticals
Drug combination	**Brand name**	**Manufacturer**	
Lopinavir + Ritonavir	Kaletra®	Abbott Labs	
Lamivudine + Zidovudine	Combivir®	GlaxoSmithKline	
Abacavir + Lamivudine	Trizivir®	GlaxoSmithKline	
Tenofovir + Emtricitabine	Truvada®	Gilead Sciences	
lamivudine + tenofovir disoproxil fumarate	Temixys®	Celltrion	

Table 1.
Market Available ARV drugs for HAART.

3. World of Nanobiotechnology in field of drug delivery

The field of Nanobiotechnology that emerges with the great modern manufacturing for higher performance of drug due the scope of the Nanoscale process (1-100 nm). With the advent of nanotechnologies, it revolutionizes drug delivery in the field of pharmaceuticals. The fundamental theory is to modulate the pharmacokinetics of the chemical molecule that has deserved to eliminate HIV from the body without damaging the body. It also increases the bio-distribution and bioavailability of the drug to expose the virus particle for a longer duration with a higher goal precision. Being Nano-sized, the Nano-material drug reacts differently than the conventional drugs, because of their decrease in scale and, they have a healing impact within the living environment.

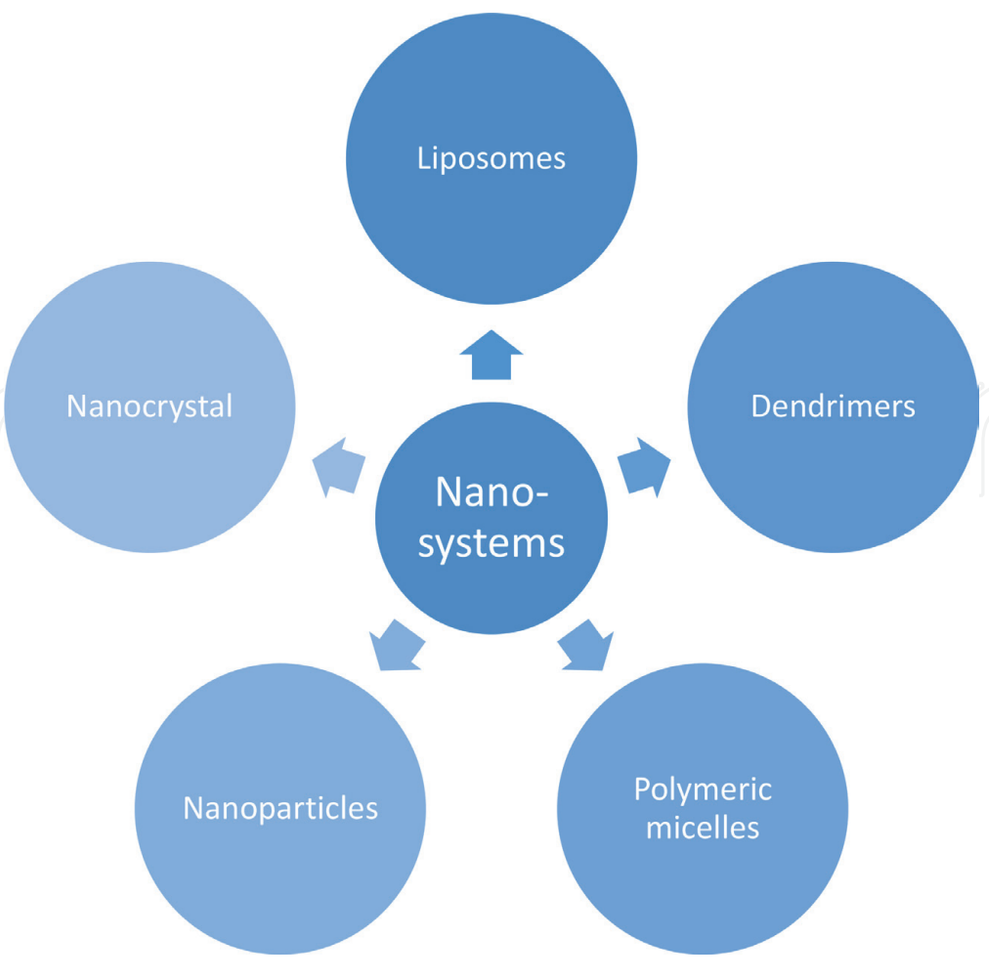

Figure 3.
Pictorial representation of Different Nano-systems.

The encased drug carried by the Nano-systems governs its, absorption, distribution, and excretion on the basis of its surface charges present on the Nano-systems due to its physical and chemical properties [20, 21]. Application of nanotechnology to the delivery of ARV drugs Holds the potential to treat AIDS and it could be beneficial Drugs at the anatomical reservoir site and also raise the half-life of drugs [22]. It has become possible to use nanotechnology for increased delivery of badly water-soluble drugs, selective delivery of drugs to particular cells or tissues, Intracellular transmission of macromolecules [23]. Nano-carriers give a range of advantages, such as control of drugs degradation, drug specificity and delivery of biological products molecules, such as proteins, peptides, oligopeptides, oligonucleotides, etc. Nanocarriers are now using it to solve the limitation of therapeutic uses, such as drug delivery, bioavailability of drugs, drug conformation stability, physicochemical stability, improved transmission permeability, drug clearance, cellular absorption, reduction of immunogenic reaction (**Figure 3**) [24, 25].

Different Nano-system strategies can be utilized as shown in the Error: Reference source not found for ARV drug entrapment which holds to cure HIV infection.

4. Liposomes

Liposomes became the first type of Nanomaterial in 1976, functionalized for drug delivery applications [26]. A liposome is a tiny microscopic vesicle that is made up of the phospholipid bilayers that are normally encircled by the watery centre. It is beneficial to hold hydrophilic drugs by trapping with in the centre, while the hydrophobic drug is inserted into the lipid bilayer [27]. The scale of the liposomes can be between 25 nm and multiple microns, offering the benefit of permeability (**Figure 4**).

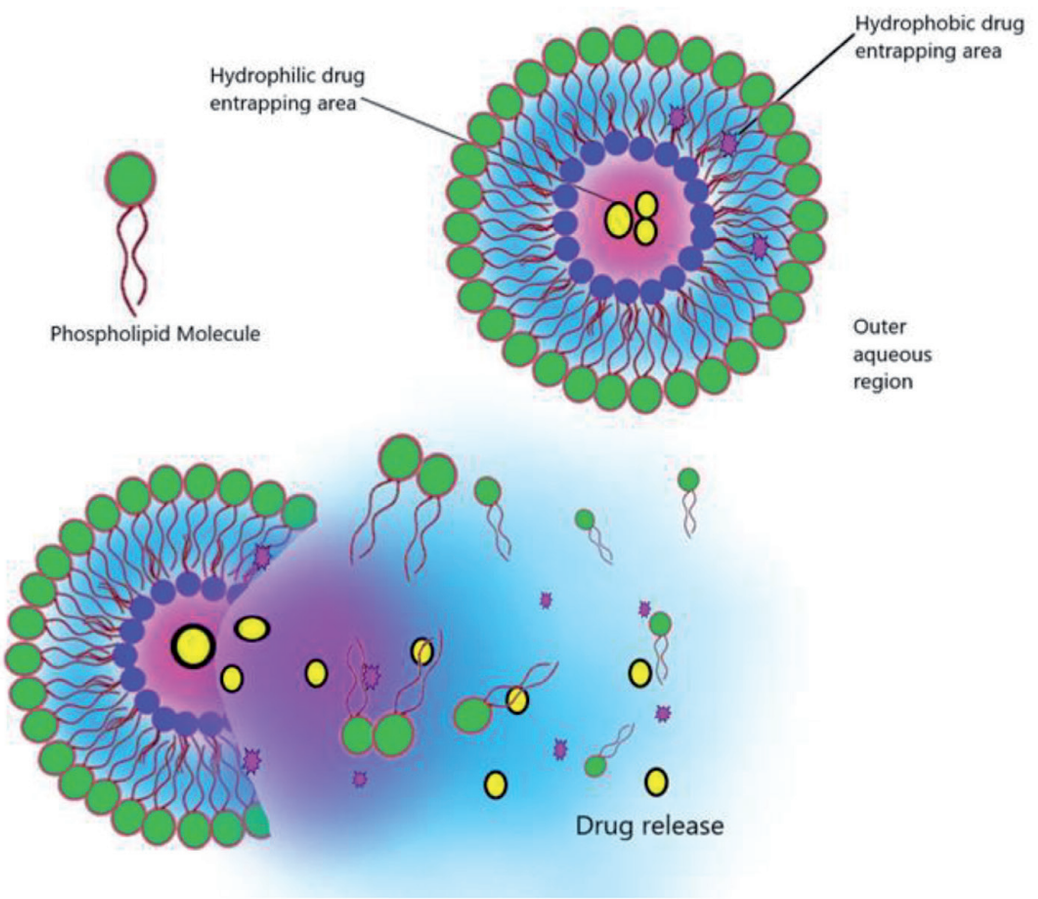

Figure 4.
Pictorial art of Liposomes for targeted drug delivery.

Human or synthetic phospholipids, along with cholesterol and additionally lipids, protein or peptide fragments, are used in their preparation. Liposomes, upon entering the living organism, realize that they are alien particles surrounded by mononuclear phagocytic cells, such as macrophages, so that liposomes are a beneficial carrier of the anti-HIV drug to the infected cell. As a result, liposomes can increase the effectiveness of the anti-HIV medication by lowering its side effect [28]. There are three types of liposomes, namely small uni-lamellar vesicles, large uni-lamellar vesicles, and multi-lamellar vesicles. In their natural form, liposomes are trapped by the reticulo-endothelial system and easily clear from circulation. Liposomes interact with the cell surface in a number of ways. The first is lipid exchange, which helps to exchange lipid molecules between liposomes and cell membranes. The second is adsorption, which diffuses across the cell membrane in the encapsulated substance within the liposome. Third, liposomes can, by fusion, transfer their encapsulated material to the cell membrane [29]. And foremost important characteristic of liposomes, it is engulfed up by the cell through endocytosis [30].

4.1 Liposomal ARV drug formulation for anti-HIV effect

Zidovudine drug is reverse transcriptase inhibitor which is amphiphilic drug, loaded into liposomes resulted in major improvements in the pharmacokinetic properties and distribution of tissues, including higher levels of distribution in reticulo-endothelial system and brain organs, longer half-life and lower average clearance of it relative to conventional zidovudine solution. Therefore, the approach to pro-drug liposomes can lead to reduced toxicity and improved efficacy of zidovudine-based HIV therapy [28]. The liposomal loaded zalcitabine system (2′,3′-dideoxycytidine, ddc) was examined in a mouse macrophage cell line that demonstrates high intracellular absorption due to anionic loading of liposomes [31]. The liposome of the phosphorylated form of zalcitabine, tested it in a murine-acquired immunodeficiency syndrome model that arrays chemical stability, improved retention entrapment, and decreased viral load in the mononuclear phagocyte system in both spleen and bone marrow [32]. Several in vitro and in vivo experiments have been undertaken by trapping ARV drugs such as acyclovir, indinavir, zidovudine, and lamivudine into the permuted liposomal structure, which shows 12 folds higher amount in blood plasma as compare to conventional drug by utilizing elastic liposomes in rat model, skin permeation of zidovudine improved 18-fold relative to simple drugs, this indicates a high effectiveness of transdermal flux relative to free drugs and higher deposition in the reticulo-endothelial organ system following the launch of zidovudine-loaded elastic liposomes trans-dermal. This suggests a greater permeability of the liposomal composition in rat model [33]. For lymphatic's targeting, the surface of liposomes was coordinated by charges and site-specific ligands to facilitate lymphatic, prominently lymph node and spleen localization. The particle-charged liposomes were formed using stearylamine, dicetyphosphate, and mannose conjugate. Evaluating these three compounds, fluorescent microscopy indicates a greater position of mannose conjugate than negative or positive liposomes, this shows the enhanced targeting of lymphatic's in AIDS chemotherapy [34]. Liposomes are quickly phagocytised by macrophages, in order to improve the extended circulation time and bioavailability of the drug the surface is changed by hydrophilic molecules such as polyethene glycol, PEGylated liposomes with targeting ligand derived from HIV gp120 guided monoclonal antibody F10 and seen as novel approaches to the battle against HIV-1. These Nano-immuno-liposomes display greater and longer antiviral efficacy than free drugs or drugs that encapsulate non-targeted liposomes [35]. Magnetic liposomes containing azidothymidine 5′-triphosphate, the average size of these magnetic liposomes 150 nm, are prepared using phosphatidylcholine and cholesterol with

a magnetite loading efficiency of 54 per cent and 45.3 per cent. It is researched to verify transmigration through the in vitro blood–brain barrier model and monocyte mediated transport by adding external magnetic field. The outcome of the apparent permeability of magnetic azidothymidine liposomes was 3 times higher than free azidothymidine [36]. Indinavir filled with mannosylated liposomes containing βD-1 Thiomannopyranoside residues covalently coupled to dimyristoyl Phosphatidyl ethanolamine (DMPE), which was also incorporated with di-steroylphosphatidyl-choline and cholesterol, was used to attack the mononuclear phagocyte function (J774.A1 macrophage cell line). This liposome showed approximately 88.7 per cent of entrapment efficacy. Important levels of the drug have been identified in macrophage rich tissues such as the liver, spleen, and lungs relative to liposomes and free drugs [37]. Cell-derived liposomes demonstrate greater and more effective targeting. It is orchestrated from the cytoplasmic membranes of the cell expressing CCR5, the human receptor for gp120 located mainly on the surface of HIV-infected cells and HIV-virion, which display a substantial 60% reduction in the viability of the HIV-infected model cell due to binding and nullifying infectivity [38]. PEGylated liposomal transmission to mammalian cells in culture demonstrated sustained release with encapsulation efficiency of approximately 33 per cent. In cell viability tests of Jurkat T- cell, lower cytotoxicity was found relative to non-PEGylated liposomes [39]. Immune-liposomes filled with heparin active serine Antithrombin III (hep-AIII) protease inhibitor injected into the non-human primate system model. The outcome indicates a steady decrease of more than 1(10) log in plasma viral load that concludes hep-AIII as a rescue or replacement agent for HIV strain immune to standard ARV drugs [40]. Glycan-Modified HIV NFL Envelope Trimer-Liposome vaccine formulation showed broad generation of neutralizing Antibody in modal, which hold proof for immunogenic vaccine development to combat AIDS [41]. The use of liposomes to prevent the spread of HIV through sexual transmission has been confirmed. The structure of the mixture consisted of liposomes that acted as decoys allowing the HIV virus to bind to liposomes instead of host cells. Some formulations contain un-conjugated liposomes whose physicochemical properties make it possible to bind to the HIV virus or to change the ligand that binds to the HIV virus has also been documented. The liposomes were created from lipids picked from the community consisting of cationic lipids, anionic lipids, neutral lipids, zwitter ionic lipids, and various combinations.

4.2 Dendrimer

The dendrimer consists of Dendron's, a small branching unit that includes an internal and a periphery end group, a polymeric nanostructure consisting of multiple branching units in a layer by layer pattern that characterizes the size, growth and microenvironment within it (**Figure 5**) [42].

Dendrimer contains space within the Dendron that can be used for drug trapping, selective drug release, defense against environmental destruction, precise targeting. Dendrimer with significant numbers of peripheral groups and inner cavities are possible vectors for chemical drugs, peptides and HIV inhibition genes. These compounds are either capable of interacting with peripheral groups or are encased in dendrimer cavities with hydrogen bonds, electrostatic and hydrophobic interactions [43, 44]. Dendrimers can improve the stability of chemical drugs and encourage cellular absorption by functional end-groups. In the case of gene therapy, Dendrimers can take the place of viruses to transfer interference genes to target cells to suppress replication of HIV. The scale of the dendrimer is less than 100 nm with less poly dispersity and higher functionality than the traditional polymer with the 3-Dimensional architecture. The kernel can be synthesized by ammonia and

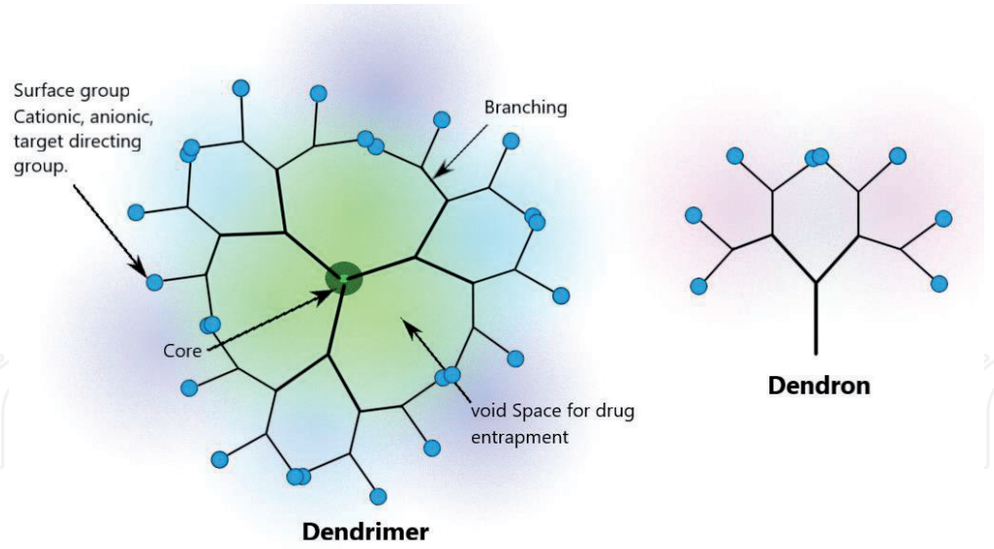

Figure 5.
Pictorial art of dendrimer complex for drug delivery.

ethylene diamine encircling highly branched repeaters such as polyether, porphyrins, poly-amido-amines, polyphenyl and polyamine acids. Core shell properties are mainly based on multivalent surfaces that contain targeting or functional groups. Dendrimers have been engineered to interact with unique functional end-groups preferably with HIV envelope proteins and receptors on host cells in order to inhibit the combination of HIV and host cells and later stages of HIV replication.

4.3 Dendrimer formulation for targeting HIV-AIDS

Following the discovery of the HIV inhibition process, two poly anionic Dendrimers BRI2932 (SPL2923) and BRI6195 (SPL6195) were found to inhibit the replication of HIV (strain IIIB) in the EC50 at 0.1 and 0.3 μg/mL, respectively, with exceptionally low cytotoxicity in the host cells. The gp120 binding assay and the virus adsorption assay showed that both substances had an effect on the docking of HIV in the host cells. In addition, higher concentrations of SPL2923 (500–2500 times EC50) could also block later stages of HIV infection. Correspondingly, the findings of cellular uptake studies revealed that SPL2923 was capable of intrusion into the host cell, while SPL6195 was not [45].

Anti-HIV medication Efavirenz loaded with tuftsin-conjugated fifth-generation poly (propylene imine) (T5PP) dendrimer, which reveals the prolonged action of the treatment in 24 hours, negligible cytotoxicity and cellular absorption 34.5-fold stronger than the free in vitro drug in infected macrophages [46]. Dendriplexes produced by 2G-NN16 and siRNAs were used for brain targeting. Transfection efficiency assessment and transcytosis by means of an in vitro blood–brain barrier (BBB) model on astrocytoma cells (U87MG). Unexpectedly, Dendriplexes developed at a ratio of 2G-NN16/siRNA of 8 displayed the highest transfection efficiency. The siRNAs-dendriplexes have been shown to effectively cross the monolayer barrier. Dendriplexes demonstrated a dose-dependent HIV inhibition of up to 85 per cent of HIV infected U87MG cells [47].

Water-stable cationic carbosilane dendrimers, which are used for drug distribution in the HepG2 cell line and PBMC, display greater interaction with nucleic acid through the development of nanoconjugates in different stable pH ranges. Nanoconjugates also display a high degree of transfection with oligonucleotide anti-HIV in laboratory settings [48]. SPL7013 is one of the anionic dendrimers that

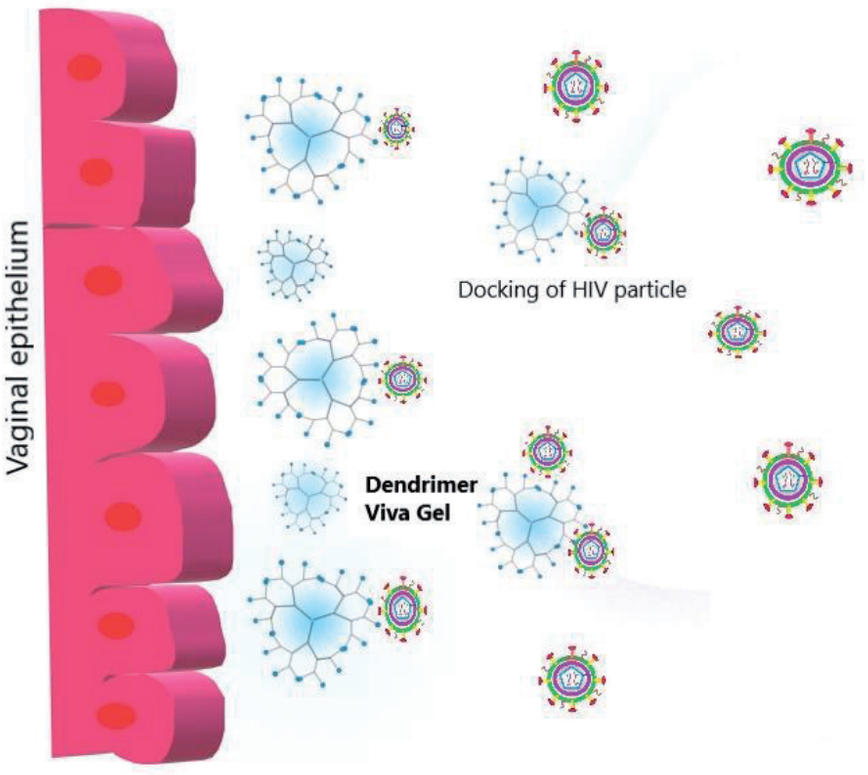

Figure 6.
Pictorial representation of working function of Viva gel, a tropical microbicide.

contains the divalent benzhydryl amide of L-lysine as the nucleus of naphthalene sulfonic acid. Efficacy tests of 5% w/w SPL7013 as an aqueous gel found that the single intravaginal dose of the formulation shielded pigtailed macaques from infection with the intravaginal (SIV) simian-human immunodeficiency virus [49]. Multivalent phosphorous-containing catanionic dendrimers with galactosyl ceramide analogs have a significant affinity to the V3 loop of the HIV-1 viral envelope protein gp120, which inhibits viral fusion with the plasma membrane and thus serves as an entry inhibitor [50]. Dendrimer may also be considered a potent factor in the selective expulsion of HIV.

4.4 FDA approved dendrimer of AIDS

A tropical microbicides, first dendrimer-based drug called VivaGel® has been submitted to the US FDA as an investigational novel drug, an aqueous-based polyacrylic acid gel containing SPL7013 buffered to physiological pH, a nanoscale dendrimeric molecule that binds to viruses and stops them from affecting the body's cells [51] as mention in **Figure 6**.

5. Nanoparticles

Nanoparticles are small colloidal particles of size ranges (10-100 nm) [52]. They have the ability for precise targeting of drugs with controlled release, depending on their size and polymer structure. Nanoparticles are expected to improve the composition and effectiveness of medications with some physiochemical weakness of low stability and solubility [53]. Owing to their scale, nanoparticle-based therapies can conveniently be performed using a range of methods (i.e., intravenous, subcutaneous, intraperitoneal) and can pass body barriers [54]. Nanoparticles have

increasingly experimented with selective delivery of ARV drugs to achieve modulated pharmacokinetics, improved potency, reduced systemic toxicity, and adverse effects.

5.1 Polymeric nanoparticles

A polymeric nanoparticle can be produced as per a favorable approach to the targeted delivery of ARV drugs. Various polymers are used for the construction of anti-HIV polymeric nanoparticles such as poly (lactic acid) (PLA), poly (lactic-co-glycolic acid) (PLGA), poly (alkyl) cyanoacrylate, poly (ethylene glycol-co-(lactic-glycolic acid)), poly(caprolactone), and poly(methyl) methacrylate. PLA and PLGA have been evaluated and considered safe for human use by the FDA. Various drugs can be integrated into these polymers on the basis of their hydrophilicity or hydrophobicity, and release properties can easily be changed on the basis of specifications.

Zidovudine-loaded polyvinylpyrrolidone (PVP)/stearic acid (SA)-polyethylene glycol (PEG) nanoparticles (PSNPs) have been formed using a solvent-emulsifying evaporation process. And tested in vitro murine neuro-2a and HeLa cells, which display substantial change in cell internalization, stable colloidal suspension, enhanced cell absorption, increased half-life, with no cytotoxicity [55]. Saquinavir-loaded poly (ethylene oxide)-modified poly (epsilon-caprolactone) (PEO-PCL) nanoparticle method using a solvent displacement technique. Cellular absorption and bio-distribution of PEO-PCL are studied in vitro in human monocyte/macrophage (Mo/Mac) THP-1 cell line, which results in a higher accumulation of drugs than in aqueous phase form [56].

Electromagnetic intrusion in the permeability of Saquinavir charged nanoparticles studied in human brain micro vascular endothelial cells. Here Nanoparticles are used as polybutylcyanoacrylate (PBCA), metylmethacrylate-sulfopropyl-methacrylate (MMA-SPM) for the study of a human blood–brain barrier model that offers higher permeability coefficient across the blood–brain barrier [57]. The Chitosan-based nanoparticles loaded with tenofovir were developed to optimize its muco adhesion. By decreasing the size from 900 nm to 188 nm of nanoparticle, non-cytotoxicity to the vaginal epithelial cell line with improved muco adhesion 6 percent to 12 percent was reported [58]. This represents polymeric nanoparticles demonstrate successful drug delivery in the fight against HIV (**Figure 7**).

5.2 Solid lipid nanoparticles (SLN) and nano-structured lipid carriers (NCL)

SLN is a thin microscopic structure consisting of physiological lipids that form stable Nanoparticles of aqueous surfactant solution. SLN provides a great opportunity to mount ARV drugs because of its small scale, high drug loading ability, slow degradation of lipid matrices, large surface reactivity. SLN also promotes sustained release, minimizing drug toxicity, dosing frequency and fluctuation of plasma drug levels. SLN shows biphasic drug release due to its composition, initial burst due to its surface adsorption, and steady release from its lipid center due to progressive degradation [59, 60]. SLN of atazanavir-name protease inhibitors was developed by Chattopadhyay et al. to verify permeability and, a blood–brain barrier model was tested on the human brain micro vascular cell line (hCMEC/D3) that successfully results from a higher accumulation of the drug by endothelial cell monolayer than the aqueous drug solution with obvious permeability across the barrier membrane [61]. Zidovudine palmitate loaded SLN, which accommodates tri laurin as a lipid center with a combination of dimyristoyl phosphatidylglycerol resulting in neutral charging. It is then modified with polyethene glycol moieties and higher surface

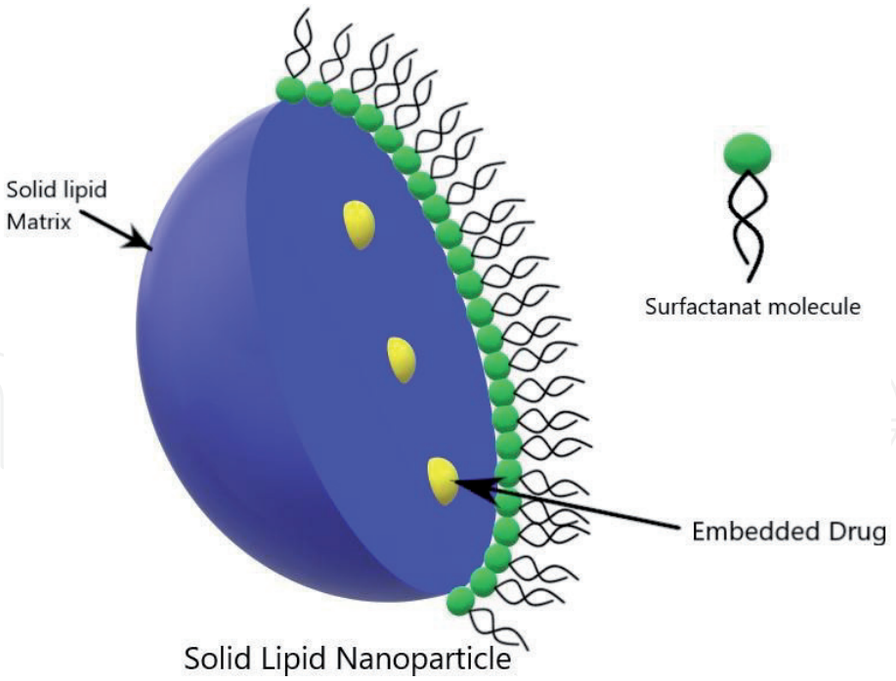

Figure 7.
Pictorial art of Solid lipid Nanoparticle carrying embedded drug.

phospholipids resulting in better plasma circulation with increased drug half-life [62]. Various changes were made to adjust the surface area of the SLN using various techniques to achieve higher drug concentration and substantial permeability through the blood–brain barrier. Lopinavir SLN was modified using a hot self-nanoemulsion technique that involves a hot isotropic mixture of stearic acid, poloxamer and polyethene glycol in water with rapid cooling, which results in increased bioavailability relative to bulk lopinavir [63]. In a perfusion trial, a high level of positively charged or negatively charged SLN will result in a high cerebrospinal cortical volume that loses the stability of the brain membrane in rats. This helps to draw attention to the fact that a high amount of surface load change in the SLN will improve the adverse impact on health (**Figure 8**) [64].

NCL is a fashioned or customized SLN with a solid lipid matrix incorporated with liquid lipids with different fatty acid chains in a compromised ordered crystalline form that provides higher drug capacity. NCL consists of low-toxic lipid molecules that have hydrolytic and oxidative stability. It also indicates the biphasic drug release potential for a liquid lipophilic surface containing a drug and a solid center with a higher melting point for drug release through diffusion and matrix erosion [65, 66]. Preferential in vitro adsorption of proteins such as Apo E to the surface of DDI-loaded NLC stabilized using Solutol® HS 15 alone or a ternary surfactant method consisting of Solutol® HS 15, Tween® 8.0 and Lutrol® F68 in vitro suggests that these NLCs can be used to target Didanosine-loaded to the brain [67]. This approach can be a big advancement and is expected to greatly change the treatment of HIV. In fact, the ability to administer ARV medications to the CNS will make it easier to treat the AIDS dementia complex of HIV/AIDS patients and thereby improve their quality of life.

5.3 Inorganic nanoparticles

This class of Nanoparticles contains metal elements such as iron, gold, silver, titanium and silica that are currently used in anti-cancer treatment, molecular labeling of biomarkers, clinical methods, bioimaging, biosensors. Noble metal

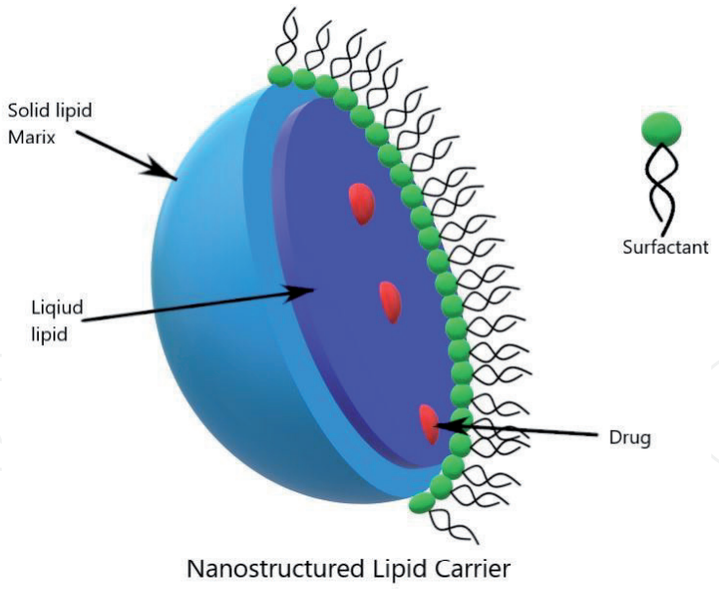

Figure 8.
Pictorial art of nanostructured lipid carrier carrying drug.

nanoparticles such as gold, silver, and platinum have been formulated using a range of techniques, such as chemical bio-reduction, rough mold, solution-phase synthesis, gas-phase deposition, and sol–gel. Silver nanoparticles are becoming more common due to their antimicrobial and antiviral effects against hepatitis B, herpes simplex virus, respiratory syncytial virus, monkeypox virus and HIV-1 in vitro, including clinical isolates and resistant strains [68–72]. Silver nanoparticles can bind to the gp120 protein and prevent viral entry, inhibit CD4-mediated viral fusion, and interfere with post-invasion phases of the HIV life cycle. Silver nanoparticles cause higher antiviral potency and therapeutic index relative to silver ion sulfadiazine salts [72]. Conjugated gold nanoparticle with TAK-779 and SDC-1721 which allow for better anti-HIV activity than its aqueous solution. Inorganic nanoparticles have limitations such as cytotoxicity, DNA damage, cellular apoptosis triggered by membrane leakage assay and LDH assay [73]. Inorganic nanoparticles usually harm the mammalian cells, because elimination of such particles from the living system is difficult and create cytotoxicity to the normal health cells with the infected cells. Some scientists are seeking to solve this issue with new ways to minimize cytotoxicity.

5.4 Polymeric micelles

Polymer micelles are nano-engineered block polymer materials that have core shells much like surfactant-based micelles and have been used to enhance permeability, aqueous solubility, chemical corrosion safety, controlled drug release, provide hydrophobic surface modification. Polymeric micelles are engineered as a hydrophobic heart and a hydrophilic shell that allows anti-HIV drugs to be trapped depending on their polarity. In addition, the surface properties of polymeric micelles, such as hydrophilic blocks, may be changed by docking antibodies or other chemical ligands unique to receptors found in diseases such as HIV-AIDS (**Figure 9**) [74].

A number of pharmaceutical scientists have formulated polymeric ARV-loaded mice, such as lamivudine conjugated with stearic acid-g-chitosan oligosaccharide mice, by esterification process that results in pH-dependent drug release, low cytotoxic activity, higher cell absorption of HepG2.2.15-infected hepatitis

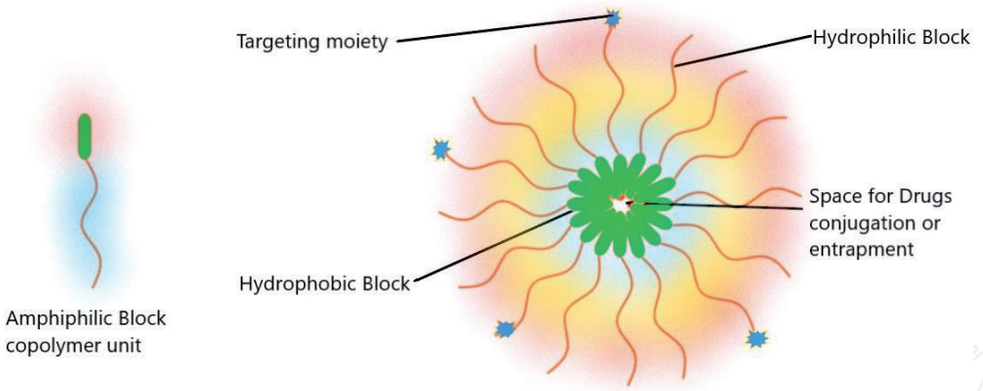

Figure 9.
Pictorial art of Polymeric micelles.

B virus-infected tumor cells [75]. Efavirenz polymeric micelles show substantial absorption rate and 3-fold improvement in the pharmacokinetic parameters of C-max from 1789 and 2657 ng/ml to 2856 and 7056 ng/ml in single doses between 20 and 80 mg/kg for healthy adult volunteers [76].

Copolymer: Poly (ethylene glycol) monomethyl ether and poly (ethylene phosphoric acid) (mPEG-*b*-PEPA) uses tenofovir, which varies in the length of the poly (ethylene phosphoric acid) chains and the degree of their saturation with tenofovir. Both adducts were found to be more active than conventional tenofovir against HIV-1IIIB in MT-4 cells; tenofovir 1:1 adduct with mPEG-b-PEPA49 displayed a 14-fold higher selectivity index. Thus, polyether–PEPA and polyester–PEPA block copolymers can well serve as scaffolds for the next generation of long-acting injectable antiretroviral formulations [77].

5.5 Nanocrystal

Nanocrystal drug itself may be a nano-sized drug particle that could be dispersed in aqueous or non-aqueous media. Drug Nanocrystals are mostly developed using approaches that promote a top-down approach or a bottom-up approach. Top-down techniques, such as media milling and high-pressure homogenization, are the most favored methods for the generation of nanocrystals because they are ideal for large-scale processing. Nanocrystal medication has longer colloidal stability, prolonged and continuous targeting due to expanded surface area. Nanoscale pure drug engineering is produced by means of an extremely hydrophobic drug that is strenuous to administer as an intravenous solution or by means of drugs with a rate of dissolution-limited oral bioavailability. Using a media milling procedure, Baret et al. formulated Rilpivirine nanocrystals of 200, 400 and 800 nm and inserted into mice and dogs via intramuscular and intra subcutaneous route and their pharmacokinetic activity was controlled. Experimentally, each therapy results in substantial detectable levels of rilpivirine up to 90 days in dogs and 3 weeks in mice suggesting success in long-term HIV prophylaxis. The author's analysis also indicates that the intra-subcutaneous route of administration shows a steady plasma concentration while the intramuscular route shows a criterion have been met as well as higher clearance. Rilpivirine amounts have also been observed in lymphoid tissues during treatment, promoting the absorption of nanocrystals by macrophages [78, 79]. Cabotegravir (CAB) is a newer drug class in the list of Viral Integrase Inhibitors, nearing to FDA approval, nano-formulated fatty acid ester CAB prodrugs administered to different strains of rats, monkey and various invitro model which,results better sustained plasma level for one year, increased

drug accumulation at lymph nodes, blood plasma, liver, enhanced cellular uptake and nanocrystal prodrug stability in macrophages, slow drug dissolution rate which suggest better half-life [80].

6. Conclusion

An empirical application for anti-HIV therapy in drug delivery system lies in the potentiality of a nanotechnology. Development of ARV drugs through nanotechnology-based system such as Liposomes, dendrimers, Nanoparticles, Polymeric Micelles, Nanovesicles, Nanoemulsion offers efficient & wide targeted drug delivery with modulated pharmacokinetics, a higher therapeutic index as demonstrated by in vitro and animal's in vivo studies. These nano-systems provide prolong drug circulation, high bioavailability, drug stability, better permeability, bioaccumulation in known reservoir sites for HIV-AIDS. It also demonstrated the application of ARV nanocarriers to deliver drugs across the blood–brain barrier and other impermeable tissue to kill HIV virus. On the basis of HIV lifecycle, diverse nanocarriers are surface modified with different moiety to prevent viral fusion with intended ARV drug delivery. The majority of works done in the field of nanocarrier ARV drug delivery system incorporate a single ARV agent. So, this chapter tends to notice about the multidrug delivery system which involves a combination of drugs can lead to tremendous efficacious treatment and downgrading of resistance profiles. Hence, nanotechnology provides a multifunctional system for scaling up therapeutic approaches with innovative formulation to fulfill diverse biological requirements.

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