IJARSCT
International Journal of Advanced Research in Science, Communication and Technology
International Open-Access, Double-Blind, Peer-Reviewed, Refereed, Multidisciplinary Online Journal
ISSN: 2581-9429
Volume 6, Issue 13, May 2026
Impact Factor: 8.2

Development and Evaluation of Novel Drug Delivery System for An Anti HIV Drugs

Kurund Dayanand Vitthal, Asst. Prof. Shubham L. Hange, Dr. Surwase K.P.
Kishori College of Pharmacy, Beed
Dr. Babasaheb Ambedkar Technological University, Lonere

Abstract: *Human Immunodeficiency Virus (HIV) remains a major global health challenge requiring lifelong therapy. Conventional antiretroviral therapy suffers from limitations such as poor bioavailability, systemic toxicity, frequent dosing, and poor patient compliance. Novel Drug Delivery Systems (NDDS) have emerged as promising approaches to improve therapeutic effectiveness, enhance targeted drug delivery, reduce adverse effects, and maintain sustained drug release.*
The present project focuses on the development and evaluation of a novel drug delivery system for anti-HIV drugs using nanoparticle-based delivery technology. The formulation was prepared using biodegradable polymers and evaluated for particle size, drug entrapment efficiency, in vitro drug release, stability, and compatibility studies. The developed system demonstrated sustained drug release, improved stability, and enhanced drug loading efficiency, indicating its potential application in HIV therapy..

Keywords: *New viruses, Challenges, Antiviral Drugs, Novel drug delivery System*

I. INTRODUCTION

Viruses are obligate intracellular parasites that largely depend on the host cell biosynthesis machinery for replication. Only a limited number of virus specific metabolic functions can be targeted by antiviral drugs without harming the host. There is a dangerous impact of viral infections globally with new viruses giving no time development of vaccines to prevent lethal effects to public. The anti-viral drugs developed against some viruses like herpes simplex virus and human immunodeficiency virus treat acute disease but do not cure latent infection, which results in recurrent chronic diseases. However, to manage the first cause it is necessary to treat with formulations of small molecules which are left as promising approach to treat viral infections and to save public life globally. Obviously, there is a need for real novel approaches for development and existence of very effective formulations of small molecules. Hence the aim of this article to present detailed account of available antiviral drugs and various approaches to design as novel drug delivery systems for effective therapy compared to conventional systems.

Novel drug delivery systems sustain the release of drug, reduce dose and frequency of administration, increases bioavailability, therapeutic efficiency and improve patient compliance. The use of nanotechnology for delivery of drugs offer unique advantages like enhancement of targeting ability of antiretroviral drugs. With the help of nanotechnology, current therapeutic drugs can now be incorporated into variety of biocompatible nanocarriers, thereby over-all pharmacological properties.

1.1 HIV AND ITS CHALLENGES

Human Immunodeficiency Virus is a retroviral infection that attacks the immune system, particularly CD4+ T lymphocytes. If untreated, HIV progresses to Acquired Immunodeficiency Syndrome (AIDS), leading to severe opportunistic infections and mortality.

Antiretroviral drugs are effective in controlling viral replication; however, conventional dosage forms have several disadvantages:

- Poor patient adherence due to frequent dosing

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- Low bioavailability
- Drug degradation
- Systemic toxicity
- Short half-life
- Poor penetration into viral reservoirs

To overcome these limitations, Novel Drug Delivery Systems (NDDS) are being developed.

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1.2 Antiviral Therapy

There are many different classes of antiretroviral drugs used to treat HIV. At least two different medications are used because attacking human immunodeficiency virus from multiple directions reduces the viral load more quickly and control the virus.

Drugs class	Brief Notes	Drug and Their Half -life (hr)
❖ Integrase inhibitors	❖ Integrase is viral enzyme that infect T cells by putting HIV DNA into human DNA. ❖ Integrase inhibitors stop the action of integrase ❖ Raltegravir was first FDA approved integrase inhibitor.	• Dolutegravir – 14 hrs • Elvitegravir – 12.9 hrs • Raltegravir – 9 hrs • Bictegravir – 18 hrs
❖ Protease inhibitors (PI)	❖ HIV needs protease to replicate in the body ❖ When protease cannot do its job, the virus can't complete the process that make new copies. ❖ Hence, protease inhibitors reduce the number of viruses that can infect more cells.	• Atazanavir – 7 hrs • Darunavir – 15 hrs • Lopinavir – 6.9 hrs • Indinavir – 1.2-2 hrs • Saquinavir – 1.5-2 hrs • Tipranavir – 5.5-6 hrs • Fosamprenavir – 7.7hrs • Nelfinavir – 3.5-5 hrs
❖ Nucleoside reverse transcriptase inhibitors (NRTI)	❖ Interrupts the life cycle of HIV. ❖ Zidovudine was first FDA approved HIV drug.	• Lamivudine – 3-6 hrs • Zidovudine – 1.1 hrs • Stavudine – 1- 1.6 hrs • Tenofovir – 17 hrs • Emtricitabine – 10 hrs • Abacavir – 1-2 hrs
❖ Non-nucleoside reverse transcriptase inhibitors (NNRTI)	❖ NNRTIs bind to hydrophobic pockets in p66 subunit of HIV-1 reverse transcriptase and induce a conformation change of enzyme structure that greatly	• Nevirapine – 25- 30 hrs • Rilpivirine – 50 hrs • Etravirine – 30-40 hrs • Doravirine – 15 hrs

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	reduces the activity	• Delavirdine – 5.8 hrs • Efavirenz – 40-50 hrs
❖ Cytochrome P4503A inhibitors	❖ CYP4503A inhibitors increases the level of certain HIV drugs (as well as other non-HIV drugs) in the body	• Cobicistat – 3-4 hrs • Ritonavir – 3-5 hrs
❖ Post attachment inhibitors	❖ Prevents HIV from entering certain immune cells.	• Ibalizumab – 40-50 hrs
❖ Fusion inhibitors	❖ HIV needs a host T cell to make copies of itself. ❖ Enfuvirtide inhibits fusion of the viral and cell membranes mediated by gp41 and CD4 interactions	• Enfuvirtide – 3.8 hrs
❖ Multi-class combination products	❖ Combine multiple medications into 1 drug form	• Lopinavir and ritonavir (Kaletra) • Atazanavir and cobicistat (Evotaz) • Lamivudine, Abacavir, Zidovudine (Trizivir)

2.3 Novel Drug Delivery System (NDDS)

Novel Drug Delivery System refers to advanced techniques designed to deliver drugs at controlled rates, targeted sites, and improved therapeutic outcomes.

Novel drug delivery systems provide successful strategies to provide long term treatment of antiretroviral drugs. Various forms include Liposomes, Microspheres, Nanoparticles, Niosomes, Emulsomes, Dendrimers, Sustained and controlled release oral formulations, implants are reported to enhance the effective delivery of antiretroviral drugs for human immunodeficiency virus therapy.

Types of NDDS Used for HIV Drugs

- Nanoparticles
- Liposomes
- Microspheres
- Niosomes
- Long acting injectable systems

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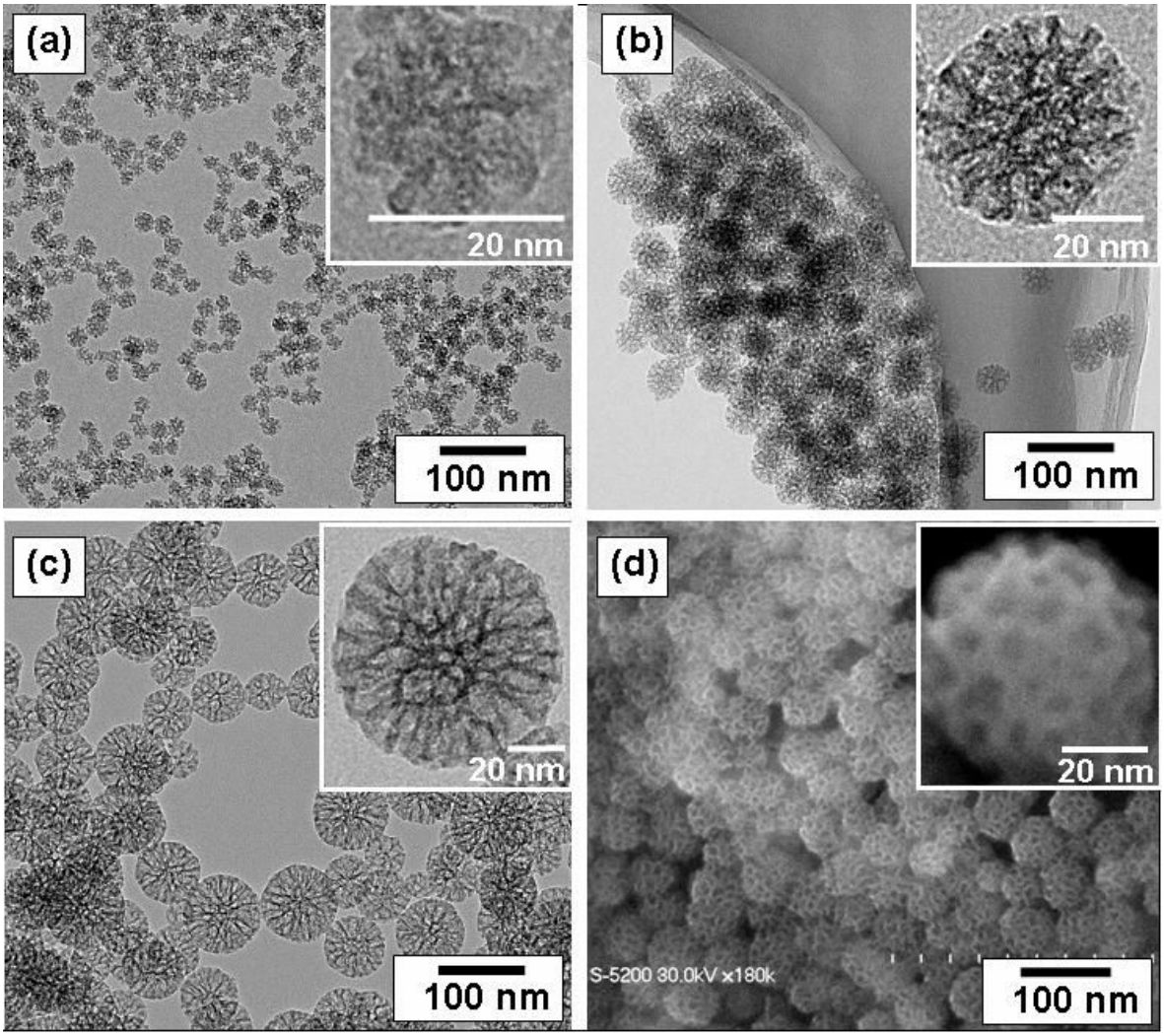
1. Nanoparticles

Nanoparticles are colloidal particles that delivers the drug to the targeted sites in the body and provides sustained drug release for prolonged period of time 19,20,21,22. Nanoparticles can be formulated for targeted delivery of antiretroviral drugs to human immunodeficiency virus infected cells. The nanoparticle drug delivery systems have advantages such as dosage reduction, decreased drug resistance and systemic toxicity.



Sr.no.	Drugs	Findings
1.	Efavirenz	Efavirenz loaded solid lipid nanoparticles formulated by solvent emulsification shows 83.75% drug release in 48 hours.

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2.	Saquinavir	Saquinavir loaded poly ethylene oxide modifies poly epsilon caprolactone nanoparticles formulated by a solvent displacement method showed sustained drug release for 24 hours.
3.	Nevirapine	Nevirapine loaded core shell gold nanoparticles were successfully formulated using double emulsion solvent evaporation method shows sustained release for a period of 24 hours.
4.	Atazanavir	Atazanavir loaded nanoparticles were formulated using thin film hydration shows significantly higher accumulation as compared to aqueous drug solution.
5.	Zidovudine	Zidovudine loaded chitosan nanoparticles formulated emulsion droplet coalescence method shows 75.89% drug release for 24 hours.
6.	Stavudine	Stavudine loaded chitosan nanoparticles were formulated. In vitro release studies showed 93% drug release in 24 hours.
7.	Abacavir	Abacavir sulphate loaded albumin nanoparticles formulated by desolvation method. The in vitro drug release for 24 hours was found to be 51.36%
8.	Lamivudine	Lamivudine loaded polymethyacrylic acid nanoparticles formulated by nanoprecipitation method shows sustained release for 24 hours.

2. Liposomes

Liposomes are concentric lipid bilayers which can be fabricated to protect molecules and to target the drugs to specific sites so these can be used as potential carriers for antiretroviral drugs. Size, charge, lipid composition affects liposomal efficiency7,8,9. Liposomes offer advantages such as drug loading both in aqueous region and within the bilayer of vesicles, protect the drug from degradation in the body, provide drug targeting. Liposomes also face some challenges with regard to antiretroviral therapy because have limited hydrophilic drug loading capacity, short shelf life, cost, poor scale up.

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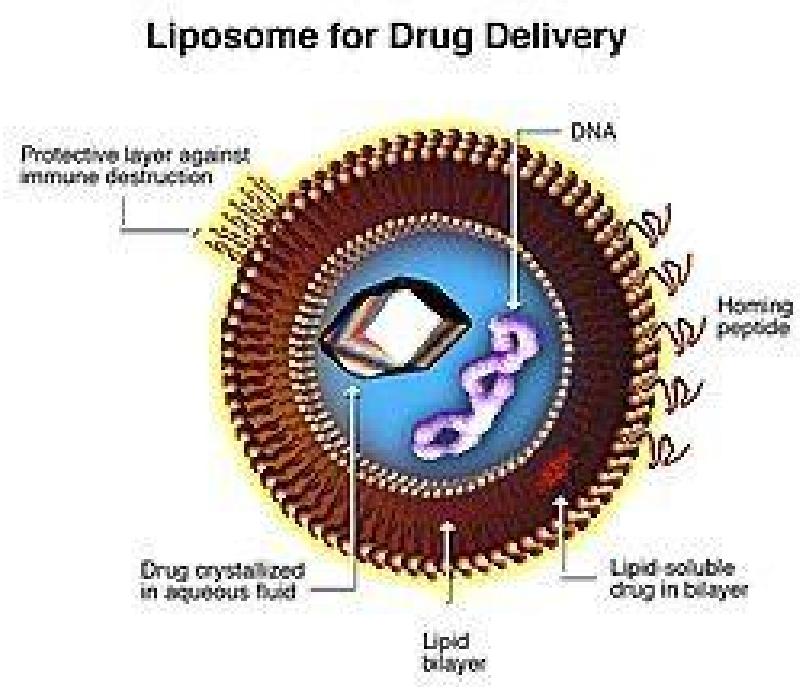
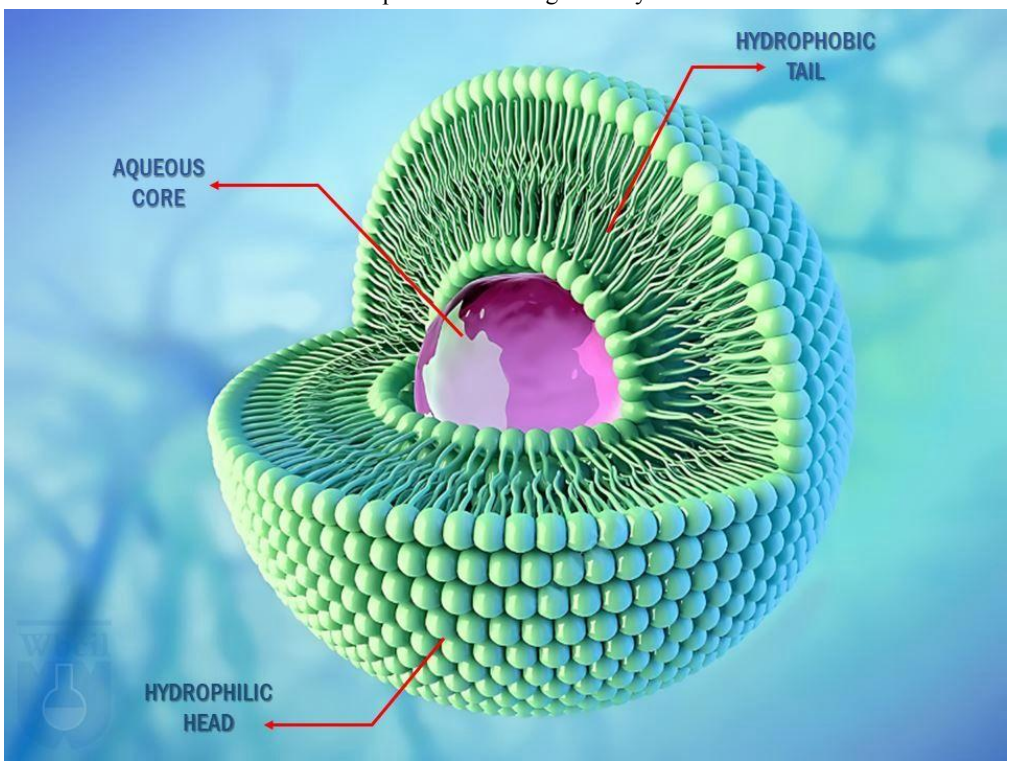


Liposomes for drug delivery



Liposomes

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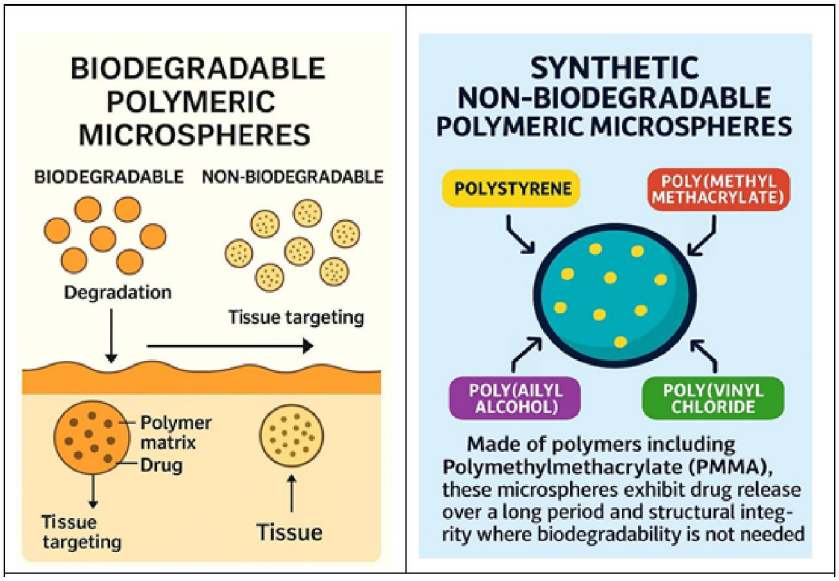
Sr.no	Drug	Findings
1	Zidovudine	Zidovudine liposomes were studied using mice model, results found that there is no bone marrow toxicity of zidovudine encapsulated in liposomes compared to free drug.
2	Nevirapine	Nevirapine liposomes were prepared from egg phospholipids using thin film hydration. Nevirapine loaded liposomal formulations improved targeted delivery of antiretroviral drug to selected compartments and cells also alleviate systemic toxic side effects.

3. Microspheres

Microspheres are systems in which the drug is surrounded by a polymer membrane. Microparticulate drug delivery systems target a particular site for sustained period of time12-14. They also have advantages like limiting the fluctuations within the therapeutic range and incorporating drug into the system without any chemical reaction.



Microspheres systems

Sr.no.	Drugs	Findings
1	Lamivudine	Chitosan with Lamivudine microspheres prepared using ionic gelation method showed 23.32- 68.72% invitro drug release.
2	Zidovudine	Ethyl cellulose and zidovudine microspheres using dry-in-oil method, good bio adhesive property was observed by invitro release.
3	Stavudine	Eudragit RS100 using Stavudine microspheres by emulsion solvent evaporation method showed 88% entrapment efficiency and buoyant for more than 12 hours.
4	Nevirapine	Nevirapine mucoadhesive microspheres were formulated by ionotropic gelation method. The entrapment efficiencies ranged from 63.50- 96.42% and controlled the nevirapine release for 12 hrs.
5	Efavirenz	Efavirenz sustained release microspheres by solvent evaporation method using Eudragit RSPO and ethyl cellulose were formulated. In vitro release studies at the end of 12 hrs shows 96.82% release.

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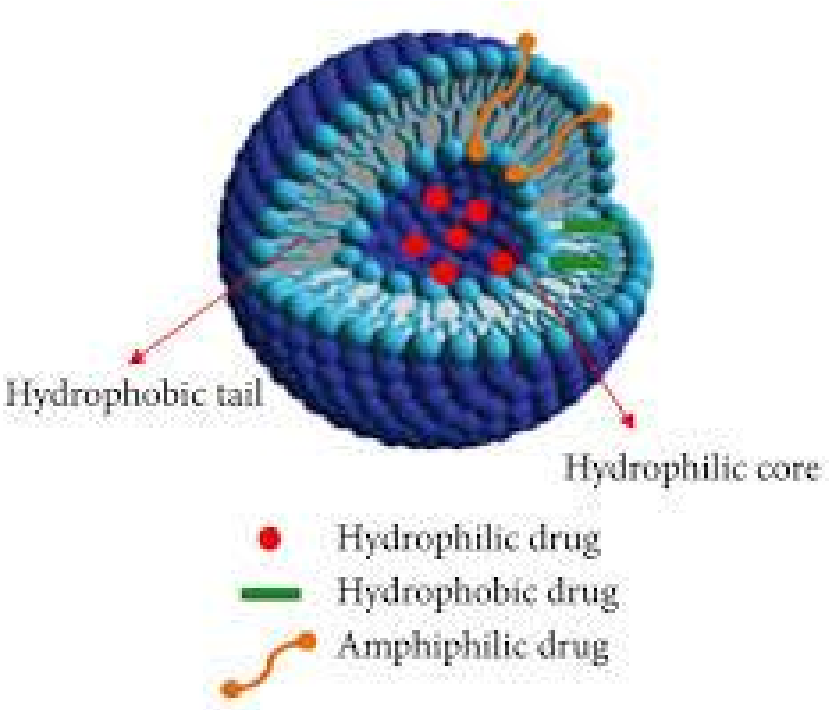
4. Niosomes

Niosomes are non-ionic surfactant vesicles obtained by admixture of non-ionic surfactant and cholesterol with hydration in aqueous media. Niosomes composed of hydrophilic and lipophilic moieties together and found to be more stable systems than liposomal drug delivery systems because of higher stability of surfactants than that of phospholipids, which are used in liposomal preparations. Niosomes found to be useful in targeted delivery of antiretroviral drugs



Niosomes A Promising Nanocarrier for Natural Drug Delivery through Blood-Brain Barrier

Sr.no.	Drugs	Findings
1	Emtricitabine	Emtricitabine niosomes formulated by thin layer evaporation (TLE) paddle stirring method. The entrapment efficiency was found to be 64.45% and enhanced the penetration of emtricitabine
2	Lamivudine	Lamivudine and stavudine were co-encapsulated in noisome with maximum entrapment efficiency 92.64%.in vitro release data showed that drug profile as zero order kinetics and drug release mechanism was diffusion. They show controlled drug release even after 24 hours.
3	Stavudine	Stavudine niosomes were formulated using ether injection method. The optimum formulation shows sustained release for 24 hours.
4	Zidovudine	Zidovudine niosomes were formulated with Tween 80 showed 88.72% entrapment efficiency. They provide controlled release of drug for a period of 24 hours

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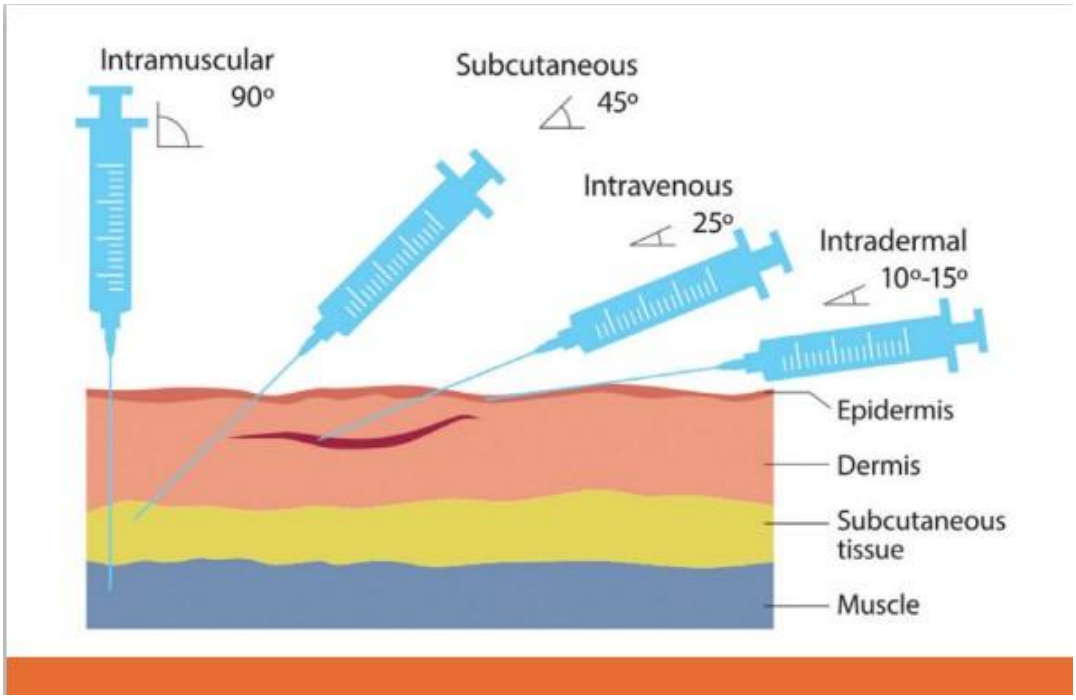
5. Long acting injectable systems

Long acting injectable formulation represent a major advancement in HIV management. Polymeric depot system and nanosuspension are currently used for long acting ART delivery.

Long-acting injectable (LAI) systems in HIV Novel Drug Delivery Systems (NDDS) replace daily oral pills with spaced-out administration (1 to 6 months). Using advanced nanomedicine and polymer depots, LAI systems significantly improve patient adherence, reduce medication fatigue, and offer discreet options for both HIV treatment and pre-exposure prophylaxis.

Long-Acting Injectable Nanoparticle Formulations



Key Technologies and Formulations

• Nanocrystal Nanosuspensions: Active pharmaceutical ingredients (APIs) are milled into nanoparticles and suspended in a liquid. This approach allows for 100% drug loading without bulky polymers, minimizing injection volume.

• Polymeric Microparticles: Drugs are encapsulated in biodegradable polymers like PLGA (poly(lactic-co-glycolic acid)), which slowly degrade in the muscle or subcutaneous tissue, releasing the antiretroviral (ARV) over time.

• In-Situ Forming Implants (ISFI): Liquid polymer solutions that are injected subcutaneously and solidify into a solid depot upon contact with body fluids, providing ultra-long-acting release profiles.

FDA-Approved Systems & Dosages

• Cabenuva (Cabotegravir + Rilpivirine): An intramuscular nanosuspension administered every 1 or 2 months for HIV treatment.

• Sunlenca (Lenacapavir): A first-in-class capsid inhibitor administered as a subcutaneous injection every 6 months for HIV treatment.

• Apretude (Cabotegravir): Administered every 2 months for HIV PrEP (prevention).

• Yeztugo (Lenacapavir): Administered every 6 months as HIV PrEP

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Benefits of HIV NDDS

• Improved Adherence: Eliminates the burden of daily dosing, which is a major barrier for many people living with HIV.

• Privacy: Decreases the visibility of treatment, reducing the stigma associated with carrying daily pills.

• Pharmacokinetic Consistency: Maintains steady therapeutic drug concentrations, reducing the likelihood of developing drug-resistant viral strains caused by missed doses

Current Clinical Challenges

• Long Pharmacokinetic Tail: Following treatment cessation, the drug remains in the body at sub-therapeutic levels for several months, risking the development of drug-resistant mutations if the patient misses subsequent therapy.

• Injection Site Reactions (ISRs): Local pain, swelling, or redness at the injection site are frequently reported, though generally mild.

• Logistical Burdens: Transitioning to LAIs requires frequent clinical visits, specialized cold-chain storage for certain formulations, and dedicated clinic staff.

Advantages

• Reduced dosing frequency

• Improved adherence

• Stable plasma drug concentration

Review of Literature

1. Elizabeth Ojewole discussed the role of novel drug delivery system in improving antiretroviral therapy. The study highlighted sustained-release tablet, nanoparticles, liposomes, emulsomes and microemulsion as potential carries for HIV drugs. The review emphasized targeted delivery to macrophages and brain tissues to improve therapeutic efficacy and reduse toxicity.

2. Alejandro Sosnik discussed the challenges associated with HIV pharmacotherapy and explained how NDDS could address issues such as poor drug penetration, toxicity, and frequent dosing. The study highlighted the importance of controlled – release system and nanocarries in HIV treatmrnt.

3. Howard E. Gendelman discussed the widely recognized for pioneering work in nanoformulated antiretroviral therapy (nanoART). He demonstrated that nanoformulated antiretroviral drugs could be taken up by macrophages and slowly released over time , improving sustained viral suppression.

4. R. Jayant contributed extensively to nanoparticle- mediated HIV therapy. His study showed that nanoparticle could improve delivery of HIV drugs into difficult to reach tissues such as the brain. The study highlighted magnetic nanoparticles, brain-targeted drug delivery , blood-brain barriesrpenetration and nano-carries for latent HIV reservoirs.

5. Omathanu Perumal worked on advanced nanofromulation for anti-HIV drugs. His research supported the use of biodegradable polymers for sustained antiretroviral delivery. His study highlighted on nanoparticle formulation development , drug targeting to HIV reservoirs and controlled – release system.

Etiology

The symptoms of HIV and AIDS vary according to the stage of the infection. One may not have any symptoms when infected with HIV for the first time, but one might develop flu-like illness 2 to 6 weeks after infection. The main signs and symptoms of the disease include-fever, headache, sore throat, swelling and redness, other illnesses if HIV persists. The virus multiplies in the lymph nodes and gradually begins to destroy the T group (CD4+ lymphocytes) and then white blood cells that make up the immune system of the whole body. There may be no symptoms for eight or nine years or more (Figure 1).

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But as the virus continues to spread and destroy the immune system, it can cause chronic symptoms such as swollen lymph nodes, diarrhea, weight loss, fever, cough and difficulty breathing. The final stage of HIV, which occurs 10 years or more after initial infection, will begin with some more severe symptoms before the disease meets the definition of AIDS. In 1993, the Centers for Disease Control and prevention (CDC) redefined AIDS as an HIV infection characterized by positive antibodies to one of the following-

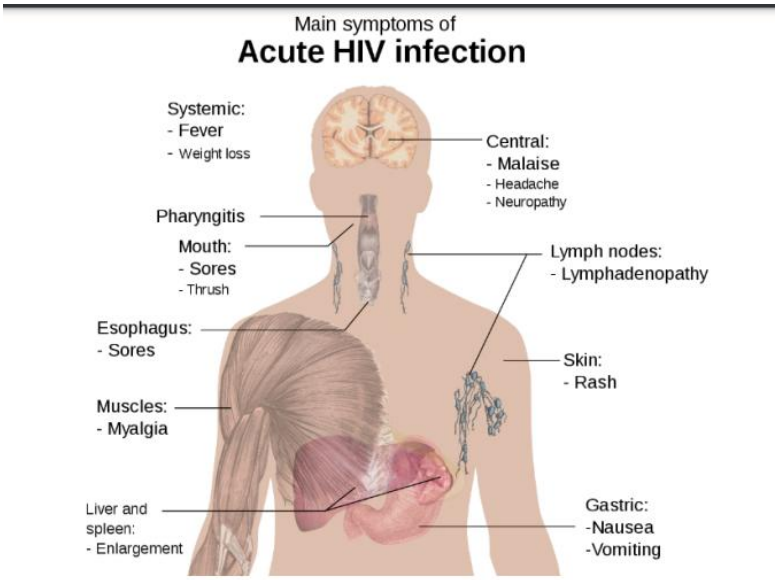
• Contagious disease exposure test

• One CD4+ lymphocyte count is 200 or less the normal range is 600 to 1000.

Table 1: Global and Indian statistics

Year	Worldwide		India	
	Cases	Deaths	Cases	Deaths
2018	37.9 million	7,70,000	23,93,672	21,571
	(32.7 million-44.0 million)	(5,70,000-1.1 million)	(19,85,744-28,97,558)	(17,141-27,586)
2019	38.0 million	6,90,000	23,92,008	21,252
	(31.6 million-44.5 million)	(5,00,000-9,70,000)	(19,84,364-28,95,545)	(16,888-27,178)
2020	37.7 million	6,80,000	23,97,884	21,084
	(30.2 million-45.1 million)	(4,80,000-1million)	(19,89,239-29,02,658)	(16,755-26,964)
2021	38.4million	6,50,000	24,01,284	20,612
	(33.9 million-43.8 million)	(5,10,000-8,60,000)	(19,92,058-29,06,772)	(16,379-26,359)

SYMPTOMS OF HIV



Pathogenesis

When infected with HIV, the virus replicates in the peripheral blood. HIV, a retrovirus which has RNA genome inserted into the host cell's DNA. Where it reproduce continously leading to cell death. HIV attaches to the lymphocytes by binding with a receptor protein CD4+ using the viral surface membrane envelope glycoprotein (GP120).

Cells with the CD4+ receptor are often called CD4+ cells or T helper lymphocytes, and these cells are the main targets of the disease. These helper T lymphocytes are used to activate and regulate other cells of the immune system, such as beta lymphocytes (antibody-producing), macrophages, and cytotoxic (CD 8+) T lymphocytes. The gradual reduction in CD4+ cell population results in failure of immune function, especially cell mediated immunity. The impaired cell

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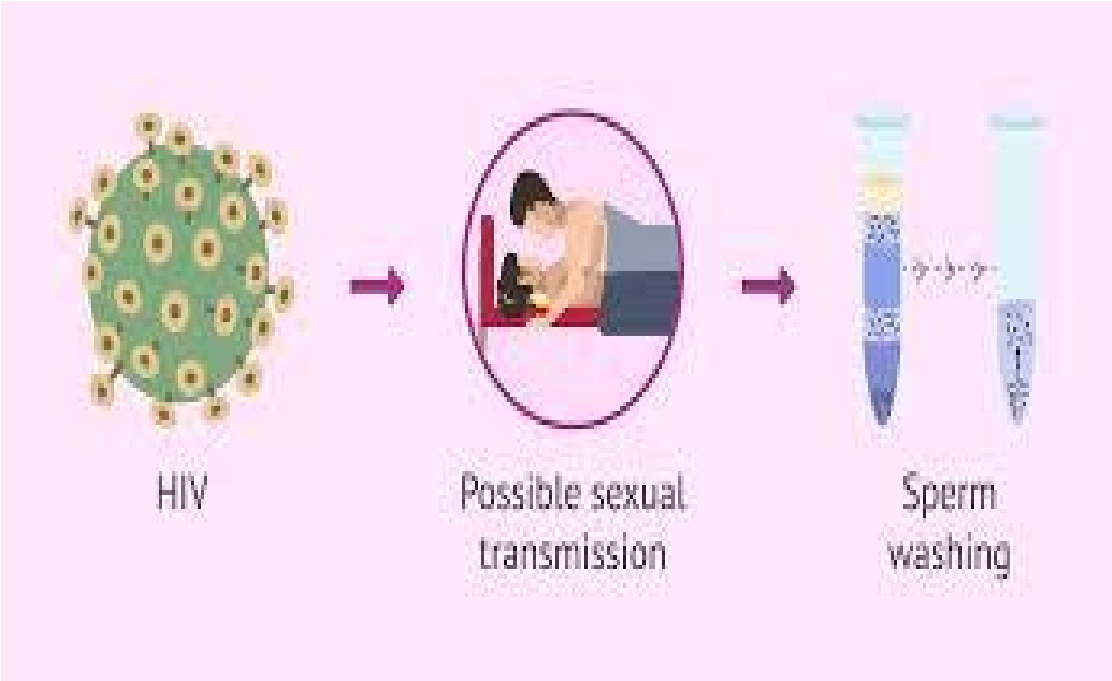
mediated immunity, which typically protects against intracellular parasites like viruses, protozoa and mycobacteria result in infection with capsulated bacteria.

Transmission

Humans are the only known reservoir of HIV and transmission of infection which essentially requires exchange of various body fluids like semen, vaginal secretions, milk or blood.

Sexual contact:

This is considered to be the best route, especially among young people (age of 15-24) who have about half or all of the new HIV infections worldwide. The presence of HIV in blood or semen helps the spread of the infection by intimate sexual contact including homosexual, bisexual and heterosexual contacts. The torn, damage to genital skin or mucous membrane, presence of other sexually transmitted diseases (e.g. syphilis), lack of circumcision in male and vigorous sexual activity facilitates the spread of infection.



Sexual transmission of HIV

Blood transmission:

Transmission via whole blood and isolated blood product is the second most frequent route. The rapid spread of infection is seen in hemophiliacs, as they regularly require blood or blood products. Intravenous drug abusers may have HIV infection as a result of the practice of "needle sharing". These people are major reason, for heterosexual transmission too.

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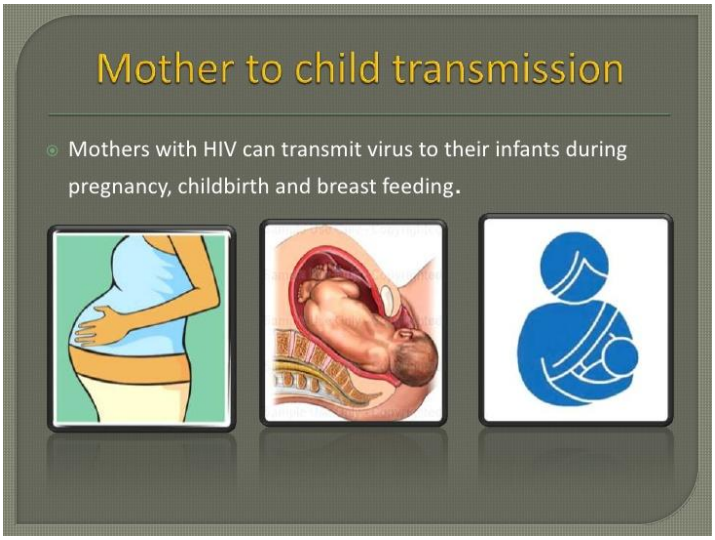
Transmission of hiv through blood

Mother to child:

Mother-to-child HIV transmission (materno-foetal transmission) can take place during pregnancy (in utero), delivery or breast feeding. The organ donation by the infected person may lead to transmission of the disease (Bodhankar SL and Vyawahare NS, 2019). In the absence of treatment, the transmission rate between mother and child is 25%. However, if there is treatment, this rate can be reduced to 1%. Breastfeeding is also a risk factor for the baby. HIV-2 is less likely to be transmitted through Mother-To-Child Transmission (MTCT) and sexually than HIV-1 (Bodhankar SL and Vyawahare NS, 2019).



Mother to child HIV transmission

Transplantation of infected tissue or organ:

The risk of transplant-related HIV infection is low. All organ and tissue donors are screened for risk factors and tested for HIV and other infectious diseases that can be transmitted through transplantation. Use of contaminated clotting factors by hemophiliacs: Hemophilia patients receiving untested and unscreened clotting factors are at extreme risk for HIV via the blood products (Jangame CM, et al., 2021)

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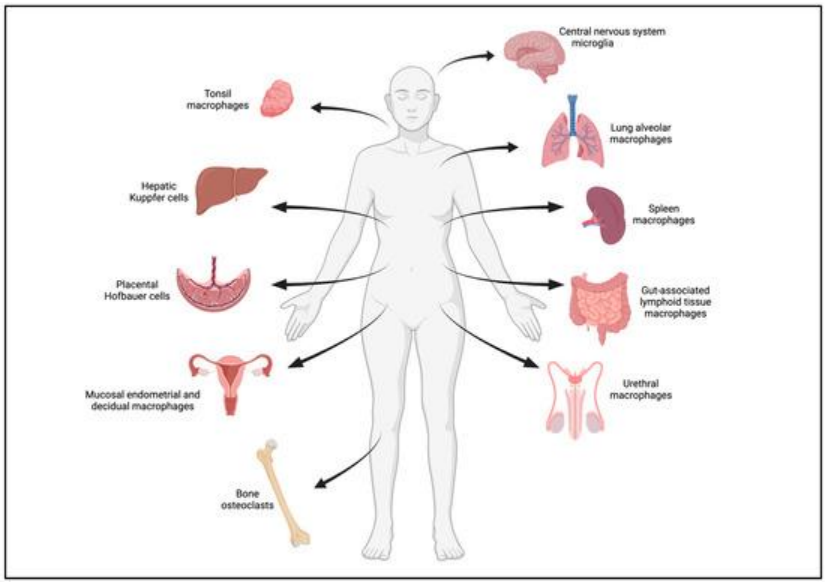

Transplantation HIV by infected tissue or organ

Clinical manifestations

The unique feature of AIDS is that the clinical manifestations are not directly caused by the causative agent but are the result of suppressed immune system. Most of the symptoms are due to secondary opportunistic infections. The appearance and severity of clinical features is variable from person to person based upon stage of the infection. Initially, infected person may be in latent period for few months, followed by development of certain manifestations like fever, tender lymphadenopathy, etc. The person in latent period can become contagious and transmit the infection. These symptoms may disappear after few days and person is symptom-free for specific duration. Some patients develop certain persistent manifestations like long lasting fever, weight loss, continuous diarrhea, oral candidiasis, multi-deramtomal herpes zoster, viral hairy leukoplakia of tongue, anemia, swollen lymph nodes and unwell feeling, later which is termed as AIDS related complex (Bodhankar SL and Vyawahare NS, 2012)

HIV infection and Acquired Immunodeficiency Syndrome (HIV/AIDS) are a group of conditions caused by retrovirus (Krämer A, 2010; Kripke C, 2007). HIV/AIDS is considered a contagious disease (Kallings LO, 2008) and studies show that HIV can be transmitted through unprotected sex. (Rodger AJ, et al., 2019). HIV is usually transmitted from mother to child through unprotected sexual intercourse (including anal and genital sex), contaminated blood, hypodermic needles, and from mother to child during pregnancy, childbirth or breastfeeding (Rom WN and Markowitz SB, 2007). Some bodily fluids, such as saliva, sweat, and tears, are not contagious. Oral sex carries a small risk of transmission (Kirti YK, et al., 2015). Without specific treatment, about half of all people will get AIDS within ten years. The most common complications are pneumocystis pneumonia (40%), cachexia as HIV wasting syndrome (20%), and esophageal candi- diasis. Other symptoms include recurrent respiratory distress (Jangame CM, et al., 2021).

Symptoms

Primary/Acute HIV:

People infected with HIV develop flu-like symptoms 2 to 4 weeks after the virus enters the body. This infection is called as initial HIV infection (infection) and it can last for several weeks.

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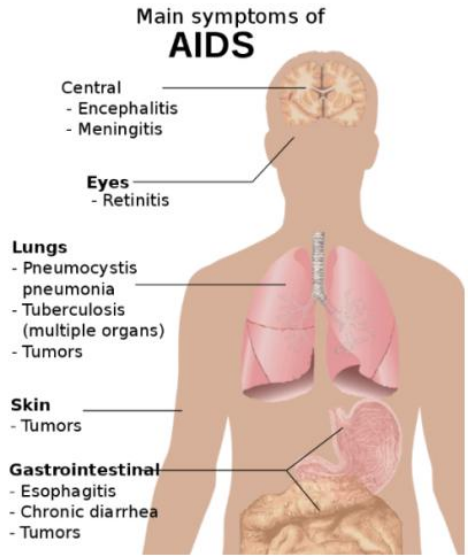
Clinical latent/Chronic HIV:

HIV remains in the body and in the white blood cells during this infection period. This phase can last for years with Antiretroviral Therapy (ART).

As the virus continues to spread and destroy the immune system, cells that help fight infection, one may have a mild infection or might experience symptoms for a long time, which is generally termed as symptomatic HIV



Main symptoms of aids

AIDS progression

Better access to ART reduces deaths. When AIDS occurs, the immune system is severely compromised, making the infected person more susceptible to infections that normally do not affect people with healthy immune systems (Chu C and Selwyn PA, 2010).

Structure of virus

It is around 100 nm to 120 nm in diameter and roughly spherical. Retrovirus is a 20 enveloped virus of the lentiviral subfamily. HIV is different from other retroviruses. There are two viral RNA strands in the nucleus surrounded by a protein sheath. The outer envelope contains a lipid matrix into which specific glycoproteins are embedded which are responsible for attachment to the cells. The outer shell of this virus contains a protein known as the envelope (env), which consists of an outer layer containing glycoprotein (gp) 120 and root gp41. The virus envelope contains HIV virus called p17 (substrate), the viral core, or the capsid, which contains another viral protein, p24 (core antigen) (Figures 3 and 4). The three main structural genes are

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International Journal of Advanced Research in Science, Communication and Technology
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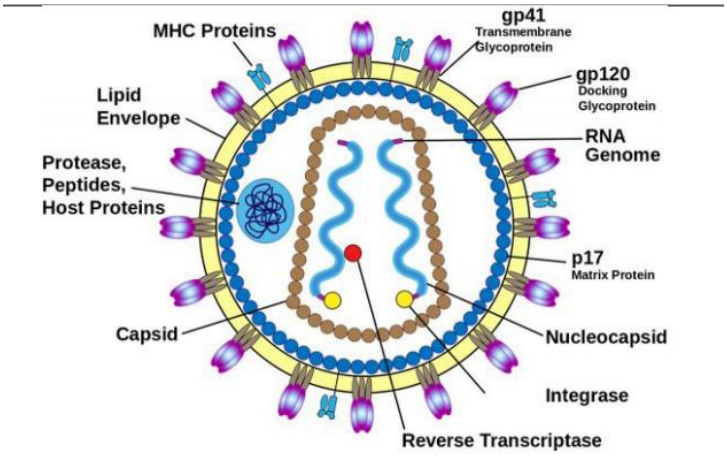
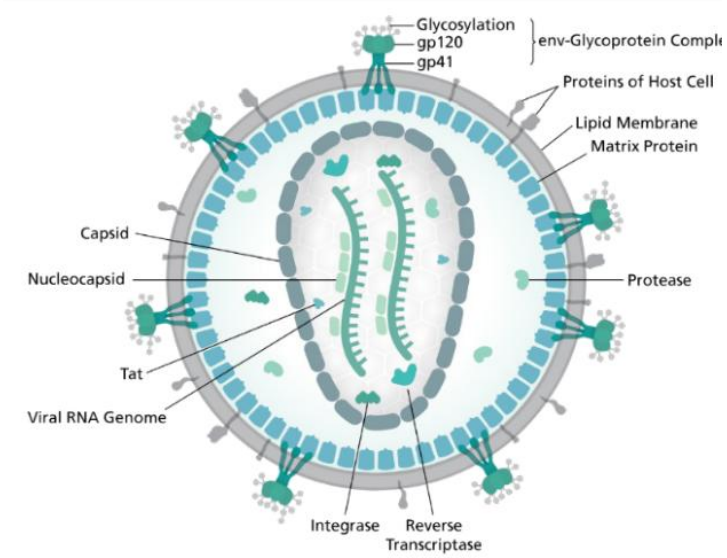
Volume 6, Issue 13, May 2026
Impact Factor: 8.2



Structure of HIV virus.



HIV virion structure

Aim & Objective

Aim :-

To develop and evaluate a novel drug delivery system for anti-HIV drugs to improve therapeutic efficacy and patient compliance Objective.

Objective :

1. To formulate nanoparticle-based anti-HIV drug delivery systems.
2. To improve bioavailability of the drug.
3. To achieve sustained drug release.
4. To reduce dosing frequency and toxicity.
5. To evaluate physicochemical characteristics of the formulation.

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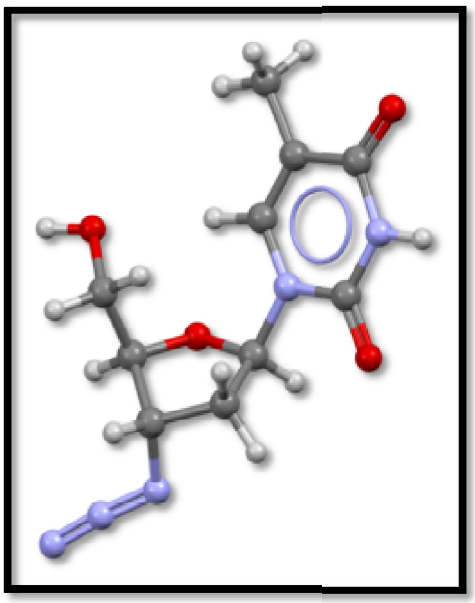
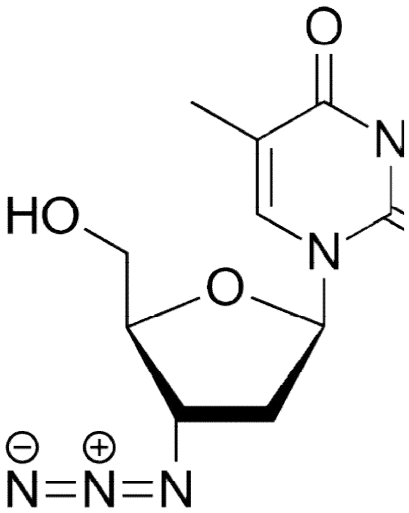
Material and Method.

Materials

Drug

Zidovudine





Polymers

- PLGA (Poly Lactic-co-Glycolic Acid)
- Chitosan

Solvents

- Ethanol
- Acetone

Ethanol

acetone

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Reagents

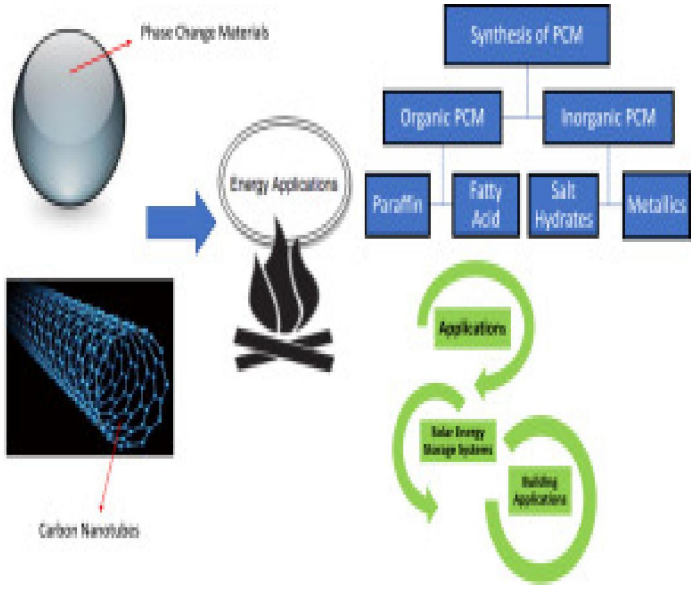
- Distilled water
- Phosphate buffer pH 7.4

Method of Preparation

Steps 1 :- Preparation of Organic Phase

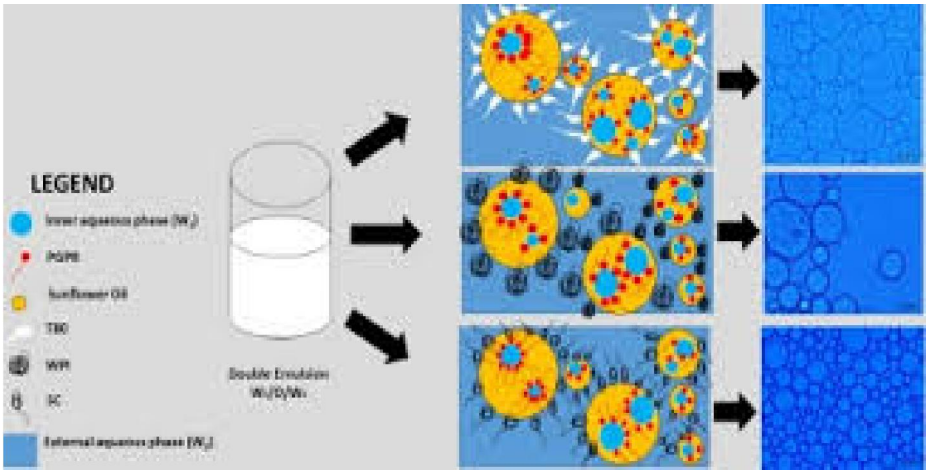
the polymer and drug are dissolved in a volatile organic solvent such as dichloromethane or ethyl acetate.

Ex. : PLGA + efavirenz dissolved in dichloromethane.



Steps 2 :- Preparation of Aqueous Phase

An aqueous solution containing stabilizer is prepared separately.



Preparing an aqueous stabilizer solution separately allows you to dissolve thickeners, surfactants, or preservatives completely without interfering with your main formulation. This minimizes clumping, ensures a homogenous mixture, and guarantees optimal pH and temperature before combining it with the rest of your batch.

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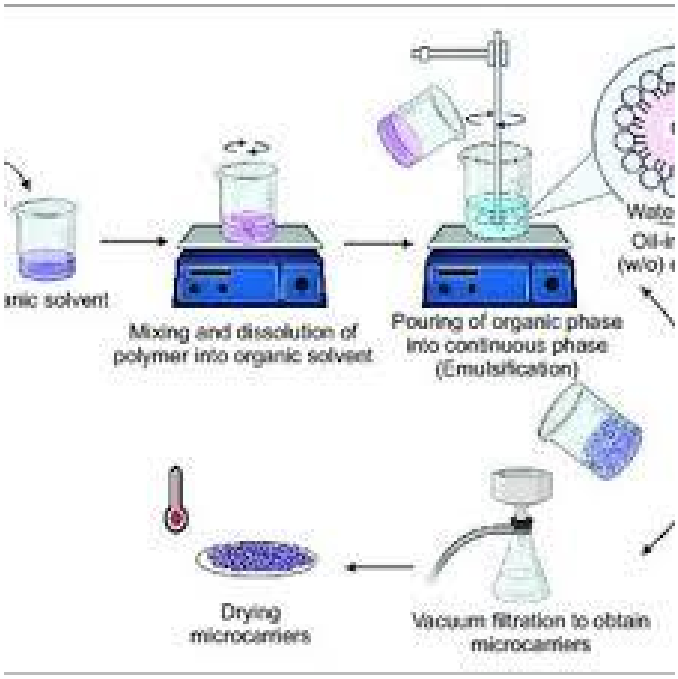
Steps 3 :- Emulsification

The organic phase is added slowly into the aqueous phase under continuous stirring or homogenization to form an emulsion.

Two types of emulsion may be formed:

• Oil-in-water (o/w)

• Water-in-oil-in-water (w/o/w)



An emulsion is a uniform mixture of two or more immiscible liquids. When creating these mixtures, the choice of emulsifier, the order of mixing, and the continuous phase determine whether the result is a simple, two-phase system or a complex, multi-layered system.

• Oil-in-water (o/w): Oil droplets are dispersed throughout a continuous water or aqueous phase. This type is primarily used for products requiring easy dilution with water, such as milks, lotions, and pharmaceutical creams.

• Water-in-oil-in-water (w/o/w): Also known as a "multiple" or double emulsion. In this system, tiny water droplets are trapped inside oil globules, which are then dispersed in a larger, continuous aqueous phase. This structure is frequently utilized in the pharmaceutical or food industries for targeted drug delivery or masking flavors

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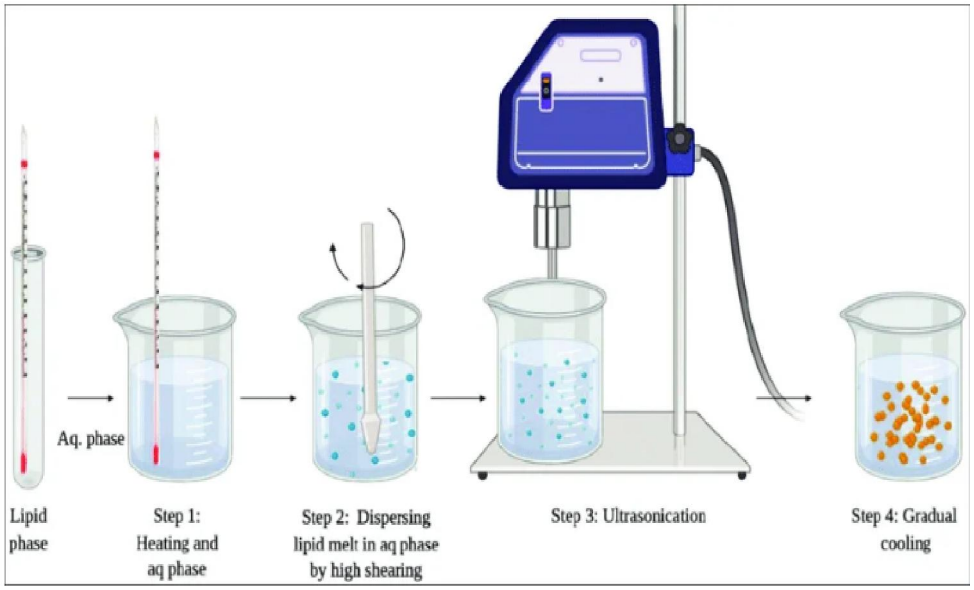
Steps 4 :- Homogenization or Sonication

High-speed homogenization or ultrasonication reduse droplet size and produces nanosized praticles.



Homogenization or Sonication

high-speed homogenization and ultrasonication are highly effective at reducing droplet size and producing nano-sized particles (typically in the 20 nm to 500 nm range) for nanoemulsions and suspensions.

• High-Speed Homogenization: Employs a rotor-stator mechanism at high speeds (often 6,000 to 25,000+ RPM) to break apart droplets using powerful hydraulic shear forces and intense turbulence.

• Ultrasonication: Utilizes high-frequency sound waves (e.g., via a probe sonicator) to generate rapid cycles of compression and expansion in the liquid. This creates microscopic bubbles that implode violently—a phenomenon known as acoustic cavitation—which shatters droplets and particles

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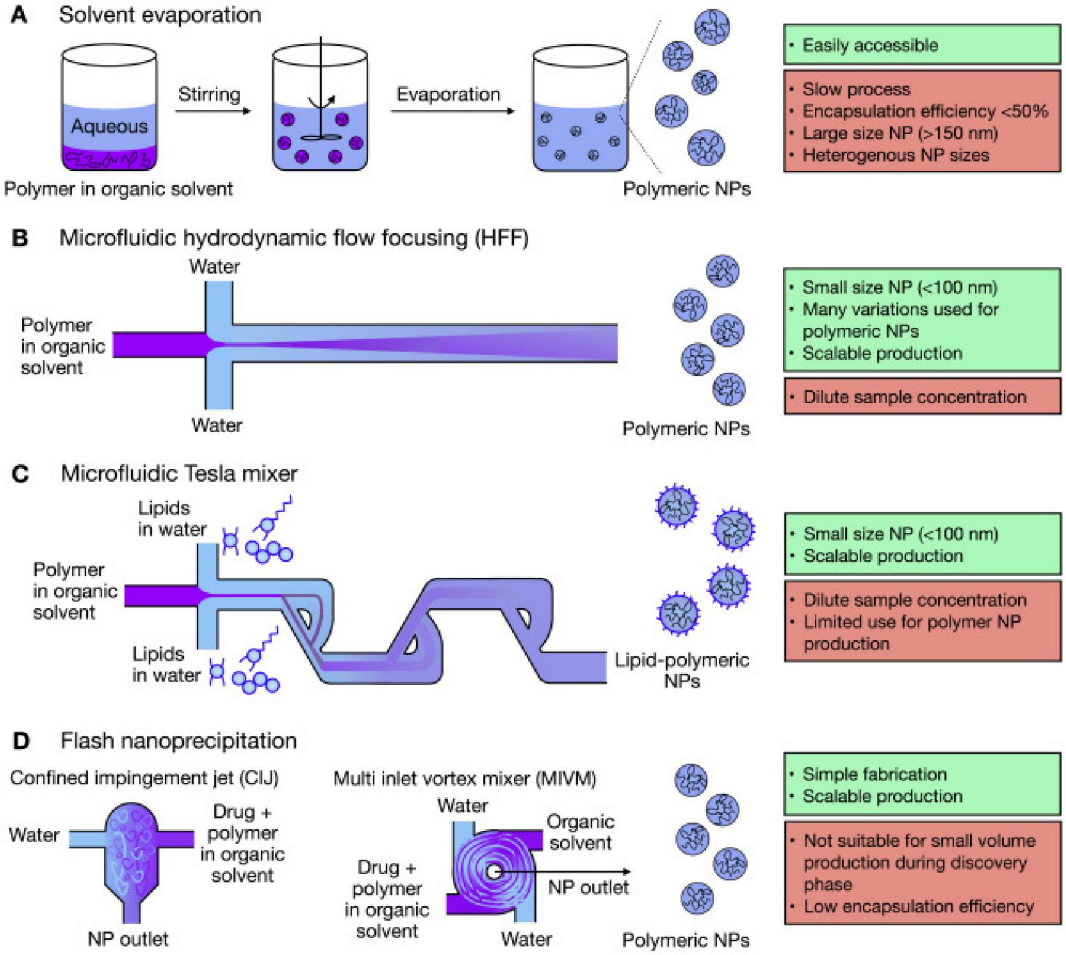
Steps 5 :- Solvent Evaporation

The emulsion is stirred continuously to evaporate the organic solvent.



As the solvent evaporates :

- Polymer precipitation
- Nanoparticle are formed
- Drug becomes entrapped inside nano particle

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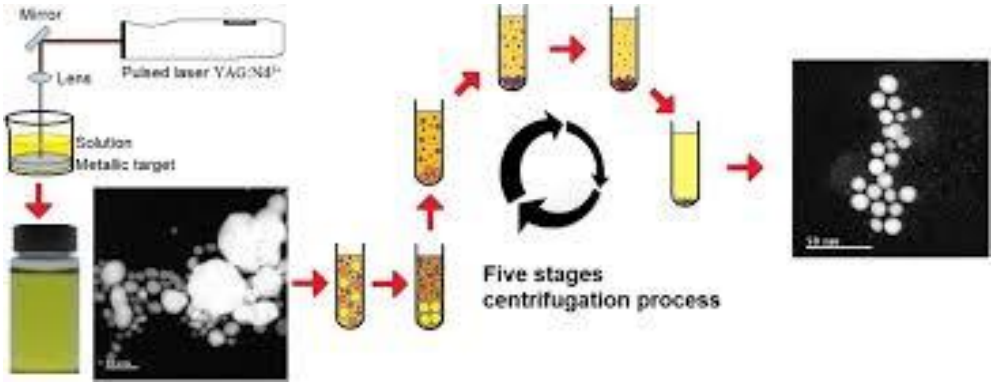
Steps 6 :- Collection of Nanoparticles
Nanoparticle are collected bye :
• Centrifugation
• Filtration
They are then washed to remove excess surfactant and unentrapped drug.



COLLECTION OF NANOPARTICLES

Nanoparticles are efficiently collected from liquid suspensions using physical separation methods like centrifugation and filtration. These techniques isolate and concentrate the particles by relying on their physical differences in size, mass, and density relative to the surrounding solvent.

Centrifugation

Centrifugation uses rapid rotation to subject the nanoparticle suspension to high gravitational forces, accelerating the sedimentation process.

• How it works: Denser or larger particles settle at the bottom of the tube (forming a pellet), while the supernatant liquid is removed.

• Techniques: Includes differential centrifugation (separating particles by size) and density gradient centrifugation (separating particles to achieve uniform, monodispersed suspensions).

• Use case: Ideal for metallic, magnetic, and polymeric nanoparticles, allowing for quick pre-concentration and buffer exchange

Steps 7 :- Drying

Nanoparticles are dried by :
• Freeze drying (lyophilization)
• Vacuum drying

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DRYING

Drying nanoparticles prevents aggregation and extends long-term shelf life.

• Freeze Drying (Lyophilization): Removes solvent via sublimation (solid to gas) under low pressure. Ideal for delicate structures, it heavily relies on excipients like sucrose to prevent nanoparticle clustering.

• Vacuum Drying: Accelerates solvent evaporation by placing the liquid slurry under a vacuum. It is often quicker and more energy-efficient, though it operates at higher temperatures.

Flow Diagram Of Solvent Evaporation Method

Drug + polymer + organic solvent
↓
Organic phase preparation
↓
Addition into aqueous phase with surfactant
↓
Emulsification (o/w emulsion)
↓
Sonification / Homogenization
↓
Solvent evaporation
↓
Nanoparticle formation
↓
Centrifugation and washing
↓
Drying
↓
Final nanoparticle product

FORMULATION DEVELOPMENT

Formulation Code	Drug (mg)	Polymer (mg)	Surfactant (%)
F1	50	100	0.5

DOI: 10.48175/IJARSCT-36077

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F2	50	150	1.0
F3	50	200	1.5

Flow Chart of Formulation

Drug + Polymer → Dissolution → Emulsification → Solvent Evaporation → Nanoparticle Formation → Drying → Evaluation

Evaluation Parameters

1. Particle Size Analysis

measured using dynamic light scattering.

Morphology

Analyzed by :

- TEM
- SEM
- AFM

2. Drug entrapment efficiency

Determines percentage of drug encapsulated.

3. In Vitro evaluation

- Drug release studies : used to determine sustained release behavior.
- Cytotoxicity studies : performed on cell lines to evaluate safety.
- Cellular uptake studies : measure intracellular delivery efficiency.
- Antiviral activity : assesses suppression of HIV replication.

4. In Vivo evaluation

- Pharmacokinetic studies :

parameter include : 1.half-life
2.bioavailability
3.plasma concentration

- Biodistribution studies :

Determine accumulation: 1.Barin
2.Lymph nodes
3.Macrop

5. Zeta potential :

Zeta potential was determined to evaluate formulation stability.

6. Stability studies :

Formulations were stored under accelerated conditions and evaluated periodically.

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RESULTS AND DISCUSSION

Result :

Evaluation results of formulation is gives below.

Parameter	F1	F2	F3
Particle Size (nm)	220	180	165
Entrapment Efficiency (%)	68	79	88
Drug Release after 24 h (%)	72	80	91

Discussion :

Increase in polymer concentration improved entrapment efficiency.

Nanoparticles exhibited sustained release behavior.

Formulation F3 showed optimal particle size and highest drug release profile.

Stability studies indicated no significant change in formulation characteristics.

The developed NDDS improved drug delivery characteristics and may enhance patient compliance in HIV therapy

II. CONCLUSION

The main intention of the paper is to highlight the potential of novel drug delivery techniques, which offer more protective and effective means of the therapy over conventional drug delivery systems. We can overcome several limitations of conventional drug delivery system such as high dosage requirement, dose frequency, low affectivity, high adverse effects by controlled and sustained release formulations. In conclusion, the most recent approaches of novel drug delivery systems for antiretroviral drugs have been found to be potentially beneficial as they have better chance to deliver a therapeutic substance to the target site in drug delivery system, to improve permeability and enhances bioavailability. The study successfully developed a nanoparticle-based novel drug delivery system for anti-HIV drugs. The formulation demonstrated Sustained drug release , Improved entrapment efficiency , Enhanced stability ,Potential for targeted delivery Thus, NDDS represents a promising strategy for improving HIV treatment outcomes.

Future Prospects

Future prospects on the development and evaluation of Novel Drug Delivery Systems (NDDS) for HIV focus on ultra-long-acting (ULA) therapies, targeted reservoir eradication, and smart nanosystems. These innovations aim to drastically reduce dosing frequency, overcome drug resistance, and improve patient adherence.

1. Key Development Directions

• Long-Acting and Ultra-Long-Acting (LA/ULA) Therapeutics:

Shifting from daily pills to sustained-release injectables or implants. Recent approvals and pipeline breakthroughs—such as twice-yearly Lenacapavir—are paving the way for advanced nanocarriers that last for months at a time.

• Targeted Reservoir Eradication:

HIV hides in cellular and anatomical reservoirs (e.g., the brain, gut, and macrophages). Future NDDS utilize surface-bound ligands (like tuftsin or mannose peptides) to deliver antiretrovirals directly to these cells, lowering overall toxicity and maximizing efficacy.

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• Viral Mimicking Nanoparticles:
Platforms such as lipid-wrapped polymeric nanoparticles and dendrimers are being designed to mimic HIV. These can bind to host receptors and prevent viral entry or cell-to-cell fusion.

• Co-Delivery Strategies:
NDDS are being engineered to simultaneously carry multiple antiretroviral (ARV) drugs and immunomodulators, allowing for synergistic multi-drug therapy from a single delivery platform.

2. Clinical Evaluation and Challenges

• In Vitro and In Vivo Pharmacokinetic (PK) Modeling: Preclinical evaluation utilizes advanced \(PK \div PD\) models to track how nanocarriers cross anatomical barriers (e.g., the blood-brain barrier) and sustain drug release without leaching.
• Nanotoxicity and Immunogenicity Assessment: A major hurdle in the clinical evaluation of NDDS is the long-term toxicity of nanomaterials and polymers. Safety profiles must be established for both the carrier materials and the degradation byproducts.
• Scalability and Manufacturing: Translating these complex formulations (like liposomes and niosomes) from benchtop laboratory scales to mass, cost-effective pharmaceutical production requires rigorous quality-by-design (QbD) evaluation.
• Alternative Administration Routes: Clinical trials are testing transdermal patches, buccal films, and vaginal/rectal microbicides for pre-exposure prophylaxis (PrEP) to provide discreet and user-controlled prevention options.
The management of Human Immunodeficiency Virus (HIV) has undergone one of the most dramatic transformations in modern medical history. The advent of Combination Antiretroviral Therapy (cART) altered the clinical trajectory of HIV, shifting it from a terminal diagnosis to a manageable chronic condition
Standard oral regimens—typically consisting of a multi-drug backbone combining nucleoside reverse transcriptase inhibitors (NRTIs), non-nucleoside reverse transcriptase inhibitors (NNRTIs), integrase strand transfer inhibitors (INSTIs), or protease inhibitors (PIs)—excel at suppressing viral replication, maintaining CD4+ T-cell counts, and preventing progression to Acquired Immunodeficiency Syndrome (AIDS)
Despite the high efficacy of conventional daily oral cART, the current treatment model is constrained by significant physiological, psychological, and programmatic limitations.
Adherence Demands: Maintaining strict adherence (\ge 95\%) is essential to prevent viral rebound and avoid the emergence of drug-resistant viral strains.
Stigma & Pill Burden: Long-term daily oral therapy carries a distinct psychosocial burden. "Pill fatigue" and the daily anxiety of accidental status disclosure remain prevalent concerns.
Physiological Barriers: Oral administration subjects highly potent antiretroviral (ARV) agents to variable gastrointestinal absorption, first-pass hepatic metabolism, and systemic fluctuations. This results in transient peak-to-trough plasma concentrations that can aggravate systemic toxicities or dip into sub-therapeutic windows.
Anatomical Sanctuaries: Conventional oral formulations struggle to achieve therapeutic concentrations within hidden viral reservoirs, such as the central nervous system (CNS), lymph nodes, and gut-associated lymphoid tissue (GALT).
To bypass these hurdles, advanced pharmaceutical engineering has pivoted toward the Development and Evaluation of Novel Drug Delivery Systems (NDDS). Rather than altering the underlying pharmacological mechanism of the drugs, NDDS modifies their pharmacokinetic and biodistribution profiles.
The approval of long-acting injectable combinations like cabotegravir and rilpivirine marked the first successful shift from daily oral pills to bimonthly intramuscular depots. This paradigm shift forms the baseline for next-generation HIV therapies.

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Next-Generation Nano-Formulations and Intracellular Targeting

Advanced nanotechnology aims to achieve passive or active cellular targeting, ensuring that antiretroviral agents are directly ferried to the primary sites of viral replication and latency: CD4+ T-lymphocytes, macrophages, and dendritic cells.

Polymeric Nanoparticles (PNPs)

Polymeric nanoparticles constructed from biocompatible and biodegradable matrix-forming materials like poly(lactic-co-glycolic acid) (PLGA) and polycaprolactone (PCL) allow for controlled, zero-order release kinetics .

Engineered block copolymers protect encapsulated ARVs from premature enzymatic degradation, prolong circulating plasma half-lives, and minimize systemic toxicities by narrowing the peak-to-trough concentration gap .

Active Cell-Targeting and Surface Engineering

Historically, long-circulating nanoparticles relied on surface PEGylation (polyethylene glycol shielding) to minimize opsonization and evade the mononuclear phagocyte system (MPS). However, contemporary research highlights emerging challenges with PEG, including the production of anti-PEG antibodies that accelerate blood clearance and compromise efficacy over multiple doses.

To resolve this issue, modern designs utilize alternative biomimetic polymers and zwitterionic coatings alongside active targeting ligands.

Surface-functionalizing these nanocarriers with specific ligands triggers receptor-mediated endocytosis into key target cells:

Mannose-functionalized nanocarriers actively bind to mannose receptors overexpressed on macrophages and dendritic cells, directing the carrier to major cellular reservoirs of HIV .

Peptide – Drug Conjugates (PDCs) link high-potency ARV payloads to specific homing peptides via responsive linkers (Jadhav, 2026). These linkages are engineered to cleave

Long-Acting Injectables, In Situ Depots, and Implantable Devices

In Situ-Forming Depots (ISFDs)

Unlike standard pre-fabricated monolithic matrices that require minor surgical incisions for insertion and removal, In Situ-Forming Depots (ISFDs) are administered as liquid polymer-solvent solutions.

Upon subcutaneous or intramuscular injection, phase inversion occurs: the organic solvent (such as N-methyl-2-pyrrolidone [NMP]) diffuses into surrounding aqueous tissues, causing the biocompatible polymer (typically PLGA) to precipitate and form a solid or semi-solid matrix matrix in situ

This matrix acts as a sustained-release depot, slowly liberating hydrophobic ARVs over several months as the polymer chain undergoes hydrolytic degradation .

Non-Erodible Subdermal Implants

For long-term protection spanning up to a year, ultra-precise drug delivery is shifting toward non-erodible subdermal implants fabricated from materials like poly(ethylene vinyl acetate) (PEVA) or polyurethane.

These devices leverage hot-melt extrusion or co-axial electrospinning to encapsulate high-potency ARVs (such as islatravir or lenacapavir).

By establishing a strict rate-limiting membrane or utilizing defined geometric slit pores, these implants provide highly predictable, constant-rate release profiles while avoiding the initial burst-release risks seen in early-generation matrix devices.

If an adverse event or drug toxicity occurs, non-erodible implants offer a clear safety advantage: they can be surgically retrieved to halt drug exposure immediately, a task that is virtually impossible with fragmented macro-depot injections.

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Alternative and Non-Invasive Delivery Routes

While injectables and implants significantly improve treatment adherence, they still require a clinical setting for administration.

Developing non-invasive, self-administered long-acting systems is a major focus for expanding global health access

Microarray / Microneedle Patches (MAPs)

Microarray patches represent a major advance in painless, transdermal drug delivery.

These patches feature an array of micron-scale polymer protrusions designed to penetrate the stratum corneum without reaching the underlying dermal nociceptors.

Next-generation MAPs utilize dissolving or biodegradable polymers (like hyaluronic acid or polyvinylpyrrolidone) that are heavily loaded with nano-solid ARV suspensions.

Upon application, the microneedles dissolve in the interstitial fluid of the skin within minutes, depositing an intradermal drug depot that slowly releases into systemic circulation over weeks or months.

Sustained-Release Intravaginal Rings (IVRs)

For Pre-Exposure Prophylaxis (PrEP), passive prevention is increasingly focused on the use of sustained-release intravaginal rings (IVRs). Constructed from elastomeric silicone matrices or polyurethane, IVRs provide localized, continuous mucosal protection against sexually transmitted HIV-1.

Advanced multi-channel IVRs allow for the co-delivery of hydrophobic ARVs (such as dapivirine) alongside broad-spectrum non-hormonal contraceptives, addressing multiple women's health needs within a single, user-controlled platform.

Critical Evaluation Parameters for Novel Anti-HIV Delivery Systems

Developing an advanced HIV drug delivery system requires a comprehensive evaluation framework that spans physical characterization, pharmacokinetic profiling, and specialized antiviral testing.

Evaluation Category	Critical Analytical Parameters	Primary Methodology / Instrumentation
Physicochemical Characterization	Mean Hydrodynamic Diameter, Polydispersity Index (PDI), Surface Zeta Potential	Dynamic Light Scattering (DLS), Electrophoretic Light Scattering
	Surface Morphology, Internal Matrix Architecture	Scanning Electron Microscopy (SEM), Transmission Electron Microscopy (TEM)
	Solid-State Crystalline vs. Amorphous Phase Analysis	X-ray Powder Diffraction (XRPD), Differential Scanning Calorimetry (DSC)
Formulation Efficiency	Drug Loading Capacity (\% w/w), Encapsulation Efficiency (\% EE)	High-Performance Liquid Chromatography (HPLC), UV-Visible Spectroscopy
In Vitro Performance	In Vitro Drug Release Kinetics, Sink Condition Maintenance	USP Dissolution Apparatus (IV / VII), Dialysis Bag Membrane Diffusion
Biocompatibility & Cytotoxicity	Cell Viability Measures, Membrane Integrity, Oxidative Stress	MTT/XTT Assays, Lactate Dehydrogenase (LDH) Release, ROS Quantification
In Vivo Pharmacokinetics	Maximum Concentration (C_{max}), Area Under Curve (AUC), Apparent Elimination Half-life (t_{1/2})	LC-MS/MS analysis of plasma, lymph nodes, GALT, and anatomical sanctuaries
Antiviral Performance	In Vitro Viral Suppression, Cytopathic Protection	p24 Antigen ELISA, T-cell Viral Replication Assays

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Evaluating the underlying release kinetics is essential for long-acting formulations. Researchers fit empirical in vitro dissolution data into mathematical models to determine the prevailing release mechanisms:

Where \frac{M_t}{M_\infty} represents the cumulative fraction of drug released at time t, k is the structural release constant, and n is the diffusional exponent indicating the transport mechanism.

An n value of 0.5 signifies pure Fickian diffusion through a polymer matrix, while an n value of 1.0 indicates Case II transport, where release is governed by polymer relaxation or matrix erosion. Achieving a near-zero-order profile (n \to 1.0 via controlled erosion or membrane barrier design) remains the gold standard for avoiding toxicity from initial drug bursting.

Translational Roadblocks and Comprehensive Safety Profiling

Despite promising preclinical results, transitioning complex NDDS platforms from benchtop discovery to clinical manufacturing poses significant challenges.

Scale-Up and Manufacturing Complexity

Laboratory-scale nanomedicines often rely on batch-wise formulation processes like micro-emulsification, solvent evaporation, or nanoprecipitation.

Translating these methods to large-scale, GMP-compliant production frequently introduces batch-to-batch variations in particle size distributions, encapsulation efficiencies, and polymer degradation patterns.

Furthermore, sterilizing nano-formulations presents unique challenges: gamma irradiation can degrade sensitive polymer backbones, while heat sterilization can trigger nanoparticle aggregation or premature drug leakage. This often necessitates complex, continuous processing technologies like microfluidic chips or high-pressure homogenizers to ensure uniform physical properties at scale.

Managing the Ultra-Long Pharmacokinetic Tail

A critical challenge unique to ultra-long-acting HIV formulations is managing the extended pharmacokinetic tail.

When a long-acting injection or implant nears the end of its operational cycle, drug release rates gradually decline.

This creates an extended period where drug concentrations remain sub-therapeutic but still persistent within systemic circulation and viral reservoirs.

If a patient misses their subsequent dosing window during this phase, the virus is exposed to low, selective drug pressures, greatly increasing the risk of selecting for drug-resistant mutant strains.

To counter this vulnerability, future translation strategies must implement strict clinical protocols, such as bridging patients with short-acting oral medications if a long-acting dose is delayed.

Local Biocompatibility and Injection Site Reactions (ISRs)

The chronic physical presence of large particulate masses or solid polymer implants within subcutaneous or muscular tissues can trigger a persistent foreign body response.

While acute injection site reactions (ISRs)—such as transient pain, erythema, and induration—are relatively common, long-term safety profiles must carefully evaluate the risks of chronic granuloma formation, localized tissue necrosis, and permanent fibrous encapsulation, which can alter intended drug diffusion rates.

Strategic Future Horizons

The future of HIV therapeutics is moving beyond simple passive depot systems toward smart, responsive, and fully integrated therapeutic ecosystems.

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Stimuli-Responsive "Smart" Systems"

Next-generation delivery platforms are being engineered to actively monitor and respond to changing physiological conditions:

Enzyme-Responsive Matrices: Utilizing polymer backbones that are selectively cleaved by specific biological triggers, such as elevated matrix metalloproteinases or viral proteases present during active HIV replication cycles.

pH-Sensitive Nano-assemblies: Designing nanocarriers that remain stable in systemic circulation (\text{pH } 7.4) but rapidly destabilize within the acidic environments of endosomes and lysosomes (\text{pH } 5.0 - 5.5), accelerating the release of active ARVs directly into the cellular cytoplasm.

Dual-Purpose Broadly Neutralizing Antibodies (bNAbs)

The co-formulation of small-molecule ARVs with engineered broadly neutralizing antibodies (bNAbs) represents a powerful multi-mechanistic approach.

Advanced delivery systems are being developed to encapsulate or tether bNAbs, providing a dual-action therapeutic strategy: the small-molecule ARVs inhibit intracellular viral replication, while the slowly released bNAbs neutralize free virions in circulation and flag infected cells for destruction by the host immune system.

Integrated "Shock-and-Kill" Strategies

The ultimate goal of modern HIV research is transitioning from lifelong viral suppression to achieving a functional cure. This effort relies heavily on sophisticated co-delivery architectures to execute the "shock-and-kill" strategy: By formulating latency-reversing agents and highly potent antiretroviral combinations within a single, target-selective nanocarrier, this approach ensures that whenever a latent reservoir cell is stimulated to express viral proteins, therapeutic drug concentrations are already present locally to abort new rounds of infection, gradually depleting the latent reservoir over time.

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International Journal of Advanced Research in Science, Communication and Technology
International Open-Access, Double-Blind, Peer-Reviewed, Refereed, Multidisciplinary Online Journal
ISSN: 2581-9429 Volume 6, Issue 13, May 2026 Impact Factor: 8.2

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International Journal of Advanced Research in Science, Communication and Technology
International Open-Access, Double-Blind, Peer-Reviewed, Refereed, Multidisciplinary Online Journal
ISSN: 2581-9429
Volume 6, Issue 13, May 2026
Impact Factor: 8.2

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