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NOVEL DRUG DELIVERY STRATEGIES FOR ANTI HIV DRUGS

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ABSTRACT

The Human Immunodeficiency Virus (HIV) is a pandemic which has covered the entire world. It is responsible for 12-000-15,000 or more new infections every day and the community acquiring sexually transmitted infections (STIs) are prone to easily acquire these HIV infections.

The objective of the present review is to summarize various anti-HIV drug delivery systems, along with drugs that have been developed for targeting HIV.

Novel drug delivery system gives an opportunity to bypass the shortcomings related to the anti-retroviral treatment. It helps in addressing towards the complexity of dosage form development such as instability, insolubility and limited entrapment of the drugs.

The present review highlights the prospects and **strategies** of novel drug delivery systems that may be highly useful for prevention as well as treatment of HIV infections.

Keywords: HIV, novel drug delivery systems, strategies

INTRODUCTION

HIV/AIDS continues to be one of the most challenging individual and public health concerns of our days **[1]**. According to the latest UNAIDS data, in 2018, roughly 37.9 million individuals were infected with HIV globally, while around 770,000 people died of AIDS-related illness **[1, 2]**. During that same year, an estimated 1.7 million new

infections occurred, mainly due to unprotected sexual intercourse.

HIV- Human Immunodeficiency Virus (HIV) is a retrovirus that can be subdivided into HIV-1 and HIV-2. Both types of HIV infection depletes the helper T-lymphocytes (CD4 cell/mm3), resulting in continued destruction of the immune system, leading to the occurrence of opportunistic infections and malignancies **[2, 3]**. A person infected with HIV is defined by Centers for Disease Control and Prevention (CDC) as having positive antibodies against HIV (positive HIV test), with 200 or more helper T-lymphocytes, and the absence of an Acquired Immunodeficiency Syndrome (AIDS) defining illness. By definition then, an HIV infected person with AIDS has fewer than 200 cells/mm3 CD4 cells or the presence of AIDS defining illness **[3]**.

Mechanism of HIV infection- The foremost step for the cause of HIV infection inside human body is the incorporation of viral genome into host cell, followed by replication of cells, which leads to the advanced stage condition as acquired immune deficiency syndrome **[1-3]**. The GP-120 the protein present in the virus attaches with the two transmembrane receptors of the host cell, one is CD4+ receptor and the other is either of the chemokine receptors namely CCR5 or CXCR4, or HIV macrophages or T helper lymphocytes. The final phase of this syndrome is usually characterized by a spectrum of diseases including the chances of infection caused by pnuemocytosis, carinii and mycobacterium tuberculosis, cancer and dementia **[4]**. The uncontrollable HIV-1 infection often ends with fatal results within 5 to10 years.

Pharmaco therapy of HIV- Chemotherapy has been the main mode of treatment of AIDS. The common classes of drugs that have been employed in the treatment of HIV infections are designed to inhibit a particular stage in the infectious cycle of HIV **[4, 5]**. Major sites of action of anti-HIV drugs in the virus are depicted in **Figure 1**. The major classes of antiretroviral agents that are in common use include the nucleoside reverse transcriptase inhibitors (NRTI), protease inhibitors (PI), non-nucleoside reverse transcriptase inhibitors (NNRTI) **[6, 7]**. The advent of Highly Active Anti- Retroviral Therapy (HAART), a combination of drugs that inhibit HIV-1 replication, has led to reduced viremia and the onset of opportunistic infections in most patients and prolonged survival **[6, 7]**. Table summarizes the details of Major classes of Antiretroviral agents. Summarized details of Major classes of Antiretroviral agents is classified in **Table 1**.

The development of antiretroviral drugs and the introduction of highly active antiretroviral therapy (HAART) in the mid-1990s—currently referred to as combination antiretroviral therapy (cART)—led to a dramatic shift of AIDS from a fatal disease into a chronic and often stable medical condition **[8]**. Antiretroviral Therapy (ART) including Highly Active Antiretroviral Therapy (HAART) drug regimens is widely considered to be one of the greatest achievements in therapeutic drug research having transformed HIV infection into a chronically managed disease. Unfortunately, the lack of widespread preventive measures and the inability to eradicate HIV from infected cells highlight the significant challenges remaining today **[9]**. List of shortcomings of conventional anti-retroviral therapy is summarized in **Figure 2**.

Moving forward there are at least three high priority goals for anti-HIV drug delivery research:

1. To prevent new HIV infections from occurring,
2. To facilitate a functional cure, i.e., when HIV is present but the body controls it without drugs and
3. To eradicate established infection.

Still, different challenges remain in anti-HIV drug therapy/prophylaxis, and these include the following, among others:

(i) the onset of severe adverse effects leading to the discontinuation or interruption of therapy or even prophylaxis

(ii) sub-optimal bio-distribution and pharmacokinetics, particularly in reservoir sites or mucosae involved in sexual transmission

(iii) the occurrence of viral resistance

(iv) troublesome regimens and/or drug delivery routes that lead to poor adherence by patients/users

(v) low stability and reduced shelf-life of active molecules, which may be particularly challenging in tropical climates and low-resource regions lacking adequate refrigerated distribution channels and storage

(vi) lack of suitable dosage forms for particular populations (e.g., children and women)

(vii) costly drug products that are often inaccessible to populations in need of therapy/prophylaxis

(viii) social and legal constraints resulting in poor access to and the discontinuation of anti-HIV therapy/prophylaxis

In the present review we have discussed the drug delivery strategies of anti- HIV drugs

under three broad headings such as Traditional, Novel and Nano. Also the review attempts to highlight the prospects and strategies of novel drug delivery systems that may be highly useful for prevention as well as treatment of HIV infections.

A. Traditional drug delivery strategies for anti HIV drugs and their limitations

Oral drug delivery is the most convenient and simplest route of drug administration for anti HIV drugs with the intention of releasing it in the gastrointestinal tract. Most of the conventional anti HIV agents are formulated as solid dosage forms, viz., tablets and capsules for oral use; or liquid dosage forms, viz., solutions, suspensions for oral and parenteral use. In oral delivery, anti HIV are formulated in such a way that they are protected from digestive enzymes, acids, etc. and released in different regions of the small intestine and/or the colon **[10]**. Not surprisingly, with the exception of the subcutaneous enfuvirtide, all the marketed antiretroviral agents are administered orally. While the oral dosage forms offer convenience, delivery of drugs via this route suffers from significant first pass effect, variation of absorption and degradation in the gastrointestinal tract due to enzymes and extreme pH conditions **[11]**. Traditional dosage forms and anti HIV drugs imbedded in them are listed in **Table 2**. Many of these compounds exhibit poor or low bioavailability due to various other factors, namely, physicochemical properties such as dissolution rate and solubility, or biological properties metabolism/elimination and transport barriers will substantially decrease the effective amount of drug reaching the target action site short biological half life of number of these drugs, conventional routes are inherently limited in that they cannot maintain a constant plasma level with the target therapeutic range for a prolonged duration **[10-12]**.

However, conventional (marketed) and innovative (under investigation) oral delivery systems must overcome numerous challenges, including the acidic gastric environment, and the poor aqueous solubility and physicochemical instability of many of the approved antiretrovirals. Biopharmaceutical considerations of Anti-retroviral drugs are listed **Table 3**.

In addition, the mucus barrier can prevent penetration and subsequent absorption of the released drug, a phenomenon that leads to lower oral bioavailability and therapeutic concentration in plasma. Moreover, the frequent administration of the cocktail (antiretrovirals are administered at least once a day) favors treatment interruption **[12]**. Due to virustatic nature of the drugs, they must be administered for the life of the

patient. All these therapeutic moieties exhibit dose-dependent toxic side effects such as hepatotoxicity, hyperglycaemia, hyperlipidemia, lactic acidosis, lipodystropy, osteonecrosis, osteoporosis, osteopenia, skin rashes, resulting from excessive systemic concentration, and they often require dosage reduction or even cessation of treatment, since conditions like lactic acidosis may even be fatal **[13]**.

To improve the oral performance of antiretrovirals, the design and development of more efficient oral drug delivery systems are called for. The present review highlights various novel research strategies adopted to overcome the limitations of the present treatment regimens and to enhance the efficacy of the oral antiretrovirals therapy in HIV.

B. Novel drug delivery strategies for anti HIV drugs

Development of novel drug delivery systems (DDS) represents a promising opportunity to overcome the various bottlenecks associated with the chronic antiretroviral (ARV) therapy of the human immunodeficiency virus (HIV) infection **[14]**. Basic features focused for designing of Novel Strategies for antiretroviral drug delivery is shown in **Figure 3**.

Researchers are being challenged to find new treatment strategies as the currently used drug therapies begin to fail in some patient population, reports on termination of therapy due to drug side effects are mounting, and new drug resistant strains of HIV are emerging. These strategies include a ‘‘multi-drug cocktail’’ therapy that attacks at several stages of HIV life cycle; a therapeutic vaccine which can boost the immune response against the virus; the development of a preventive vaccine based on a weakened strain of HIV, and the successful maintenance of HIV-inhibitory concentrations at target sites with minimal side effects **[15]**. To avoid hepatic first pass metabolism and intestinal degradation, efforts are being made to alter the mode and route of delivery of the drug. Delivery of nucleoside analogues through percutaneous, rectal, buccal, nasal, intrathecal routes and as coated dosage form by oral route, are being studied. Percutaneous absorption has been one of the most reported routes for non-oral administration of antiHIV agents. Also efforts have been made to design drug delivery systems for antiHIV agents to reduce the dosing frequency, to enhance the bioavailability, to improve the CNS penetration and inhibit the CNS efflux and to deliver them to the target cells selectively with minimal side effects. Amongst the recent approaches controlled and targeted delivery are the noted ones **[13-15]**. Novel Strategies designed

antiretroviral drug delivery are shortlisted in **Table 4**.

Novel drug delivery systems present an opportunity for formulation scientists to overcome the many challenges associated with antiretroviral (ARV) drug therapy, thereby improving the management of patients with HIV/AIDS. Most of these drugs bear some significant drawbacks such as relatively short half-life, low bioavailability, poor permeability and undesirable side effects. Efforts have been made to design drug delivery systems for anti HIV agents is summarized in **Figure 3**. The physico-chemical properties and the in vitro/in vivo performances of various systems such as sustained release tablets, ceramic implants, liposomes, emulsomes, aspasomes, microemulsions and nanopowders are summarized in **Table 5**.

This review article highlights the significant potential that novel drug delivery systems have for the future effective treatment of HIV/AIDS patients on ARV drug therapy

1. **Sustained release/bioadhesive/enteric coated matrix tablets-** Sustained drug delivery systems are designed to achieve a continuous delivery of drugs at predictable and reproducible kinetics over an extended period of time in the circulation. The potential advantages of this concept include minimization of drug related side effects due to controlled therapeutic blood levels instead of oscillating blood levels, improved patient compliance due to reduced frequency of dosing and the reduction of the total dose of drug administered. Bioadhesive drug delivery systems are designed for prolonged retention on the mucosa to facilitate drug absorption over a prolonged period of time by interacting with mucin.
2. **Liposomes-** These are concentric lipid bilayers and offers hydrophillic as well hydrophobic drug loading in aqueous region and within the bilayer of the vesicles respectively. These nanocarriers emerged as potential anti-HIV nanocarriers due to their property of targeting drug to HIV reservoir. Encapsulation of antiretroviral agents in to liposomes insures delivery of drug at targeted site, protects degradation of drug during circulation and improves pharmacokinetic and tissue distribution patterns of the drug. Liposome improves bioavailability and residence time of encapsulated

drug at the target site. The vesicle size, surface charge, lipid composition and methods of preparation significantly affect the liposomal drug entrapment and targeting efficiency.

3. **Dendrimer-** Dendrimer-based systems have also been explored for the concept of ARV targeting. Dendrimers are characterized as being synthetic, highly branched, spherical monodispersed macromolecules. Due to their unique architecture and macromolecular characteristics, they have emerged as an important class of drug carrier for targeted delivery.
4. **Micelles and microemulsions-** Microemulsions have been studied for ARV drug delivery as an approach to redirect the absorption of ARV from the portal blood to the HIV-rich intestinal lymphatics, thus enhancing the bioavailability of drugs that undergo extensive first pass metabolism and have poor oral bioavailability.
5. **Other routes of drug delivery of anti HIV drugs-** Studies on the potential of systems for alternative routes of ARV drug administration, i.e., transdermal, buccal and rectal, are also highlighted in table below. Table 6 contains detailed summary of Main Features & Limitations of other routes of Drug Delivery.

C. Nano strategies for anti HIV drugs

The surge of interest in nanoparticulate systems for ARV therapy has led to several drugs being studied for its incorporation **[16]**. These in vitro/in vivo studies clearly confirm the ability of nanoparticles to enhance the therapeutic efficacy of ARVs, as well as addressing formulation problems **[17]**. Targets for specific targeting of HIV infected cells are shown in **Figure 4**. While the Summary of Nano formulation approaches and their Features with specific drugs is listed in **Table 7**.

i. **Nanopowders-** Most recently, nanopowders have been used as a delivery system for oral administration to enhance the dissolution rates of poorly soluble drugs. Tween 80/poloxamer 188 stabilised nanosuspensions of the hydrophobic ARV, loviride, were prepared by media milling, and sucrose co-freeze-dried to obtain solid nanopowders.

ii. **Nanoparticles-** Drug encapsulated nanoparticles are solid colloidal particles that range from 10 to 1000 nm in size. Based on their size and polymeric composition, they are

able to target drug to specified sites in the body, and have also shown potential for sustained drug delivery. Nanoparticles have also been explored for improving the formulation and efficacy of drugs with physicochemical problems such as poor solubility and stability. They are being increasingly investigated for targeted delivery of ARVs to HIV infected cells and to achieve sustained drug release kinetics. Their encapsulation into such systems may provide improved efficacy, decreased drug resistance, the reduction in dosage, a decrease in systemic toxicity and side effects, and an improvement in patient compliance. Solid lipid nanoparticles (SLNs) are prepared from lipids that remain in a solid state at room and body temperature While the majority of studies have focused on targeted delivery of ARVs with nanoparticles, some studies have also focused on modifications to its preparation to enhance drug loading and decrease toxicity; and also to increase its absorption by facilitating pH-sensitive drug release.

iii. **Nanocontainers-** Poly propyleneimine (PPI) dendrimer, t-Boc-lycine conjugated PPI dendrimer (TPPI) and mannose conjugated dendrimers (MPPI) were synthesized and used to prepare ‘‘nanocontainers”. Like a dendritic box, these molecules act as closed containers of nanoscopic size containing the entrapped drug, and are therefore called nanocontainers. The drug entrapment efficiency of the nanocontainers varied, with the mannose conjugated dendrimer being 47.4%, followed by that of the PPI dendrimer (32.15%) and t-Boc-glycine conjugated dendrimer (23.1%).

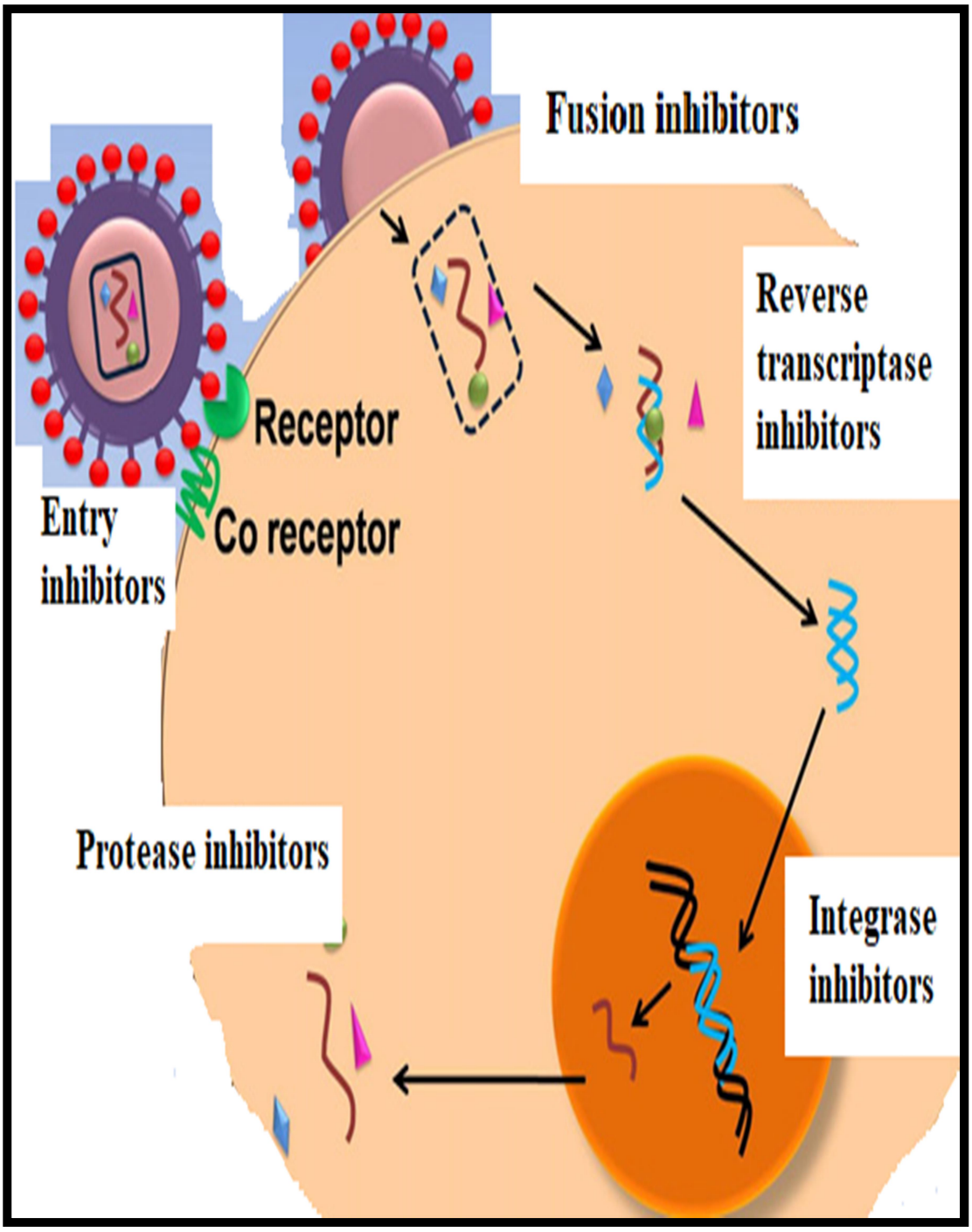

Figure 1: Major sites of action of anti-HIV drugs in the virus

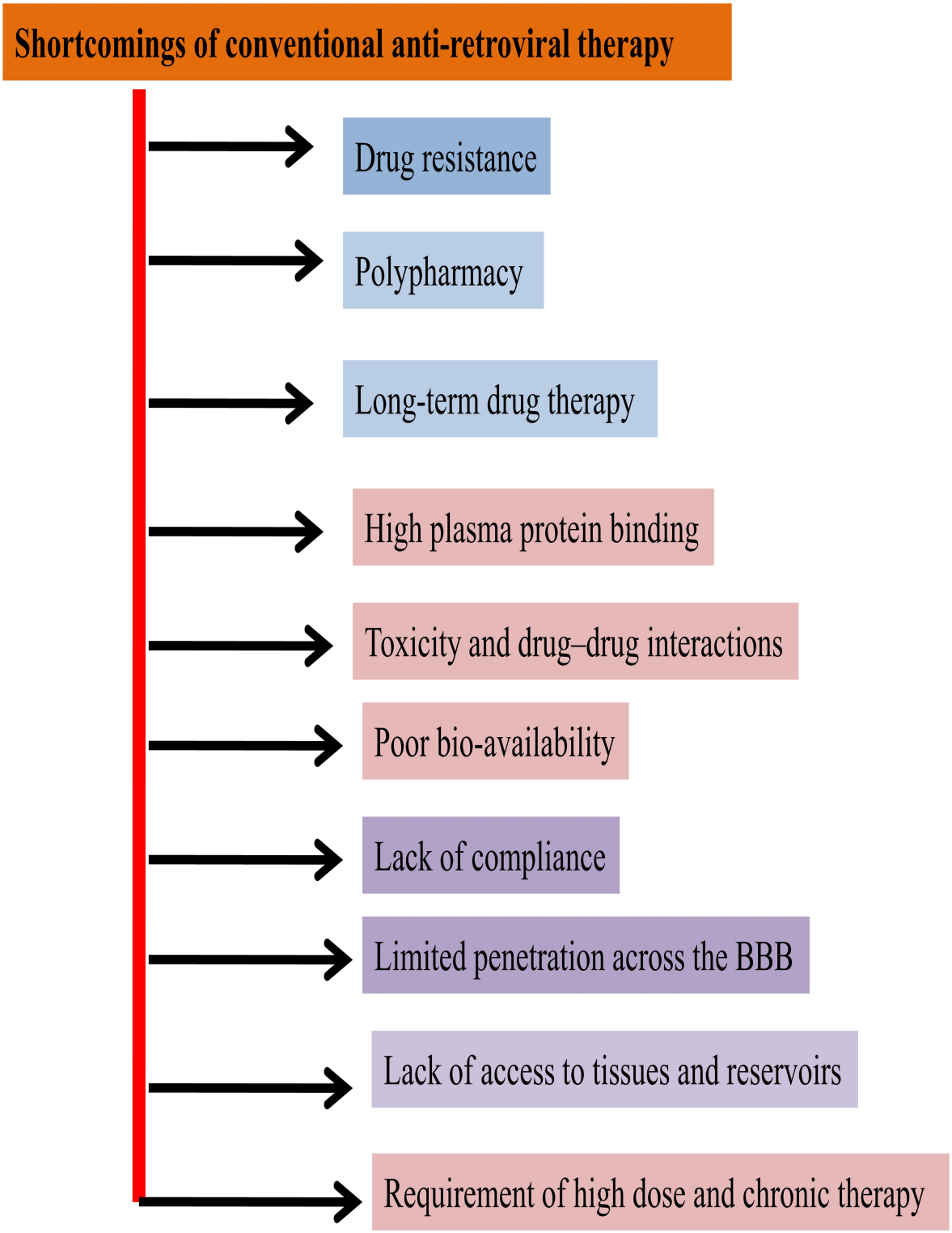

Figure 2: List of shortcomings of conventional anti-retroviral therapy

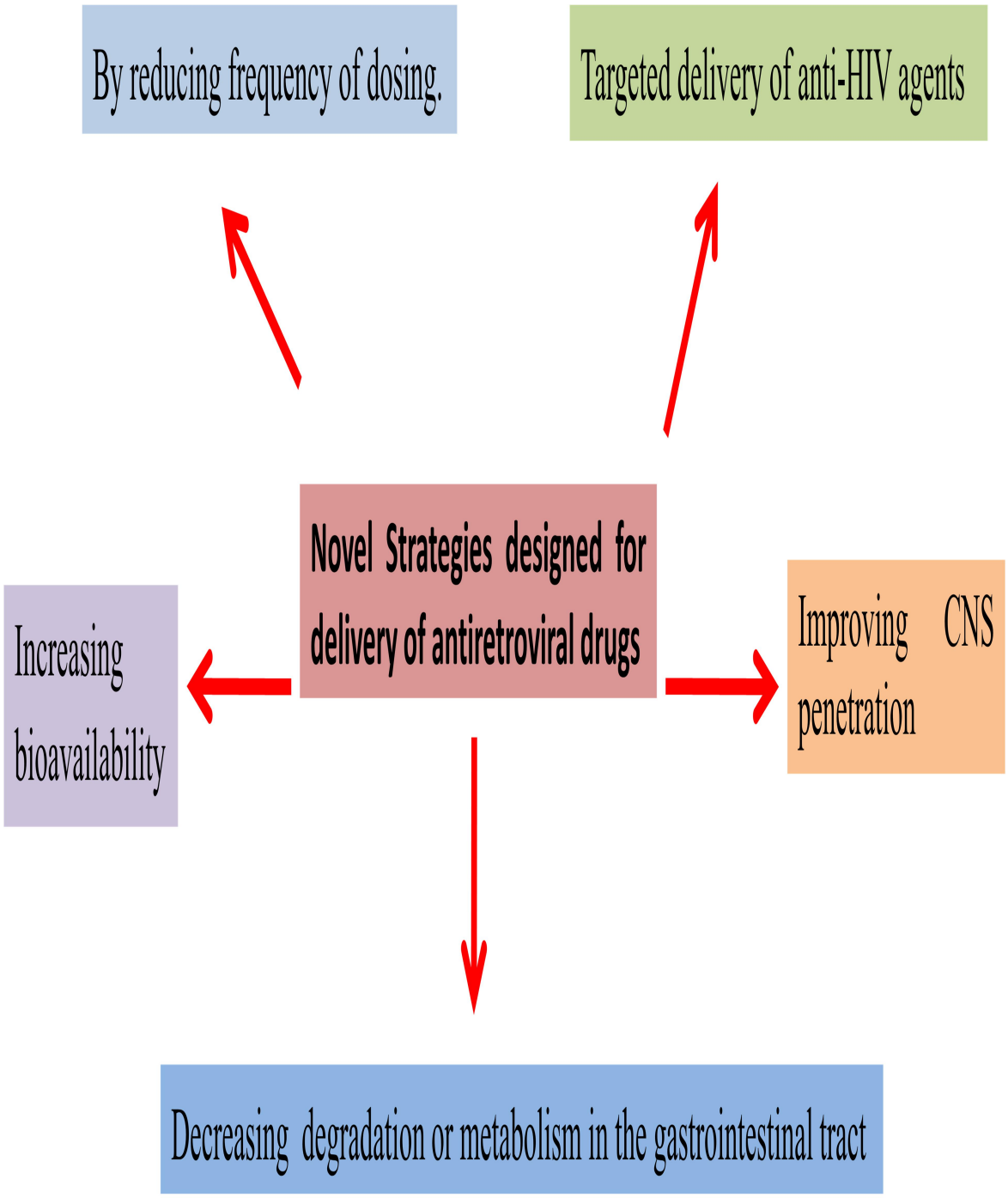

Figure 3: Basic features focused for designing of Novel Strategies for antiretroviral drug delivery

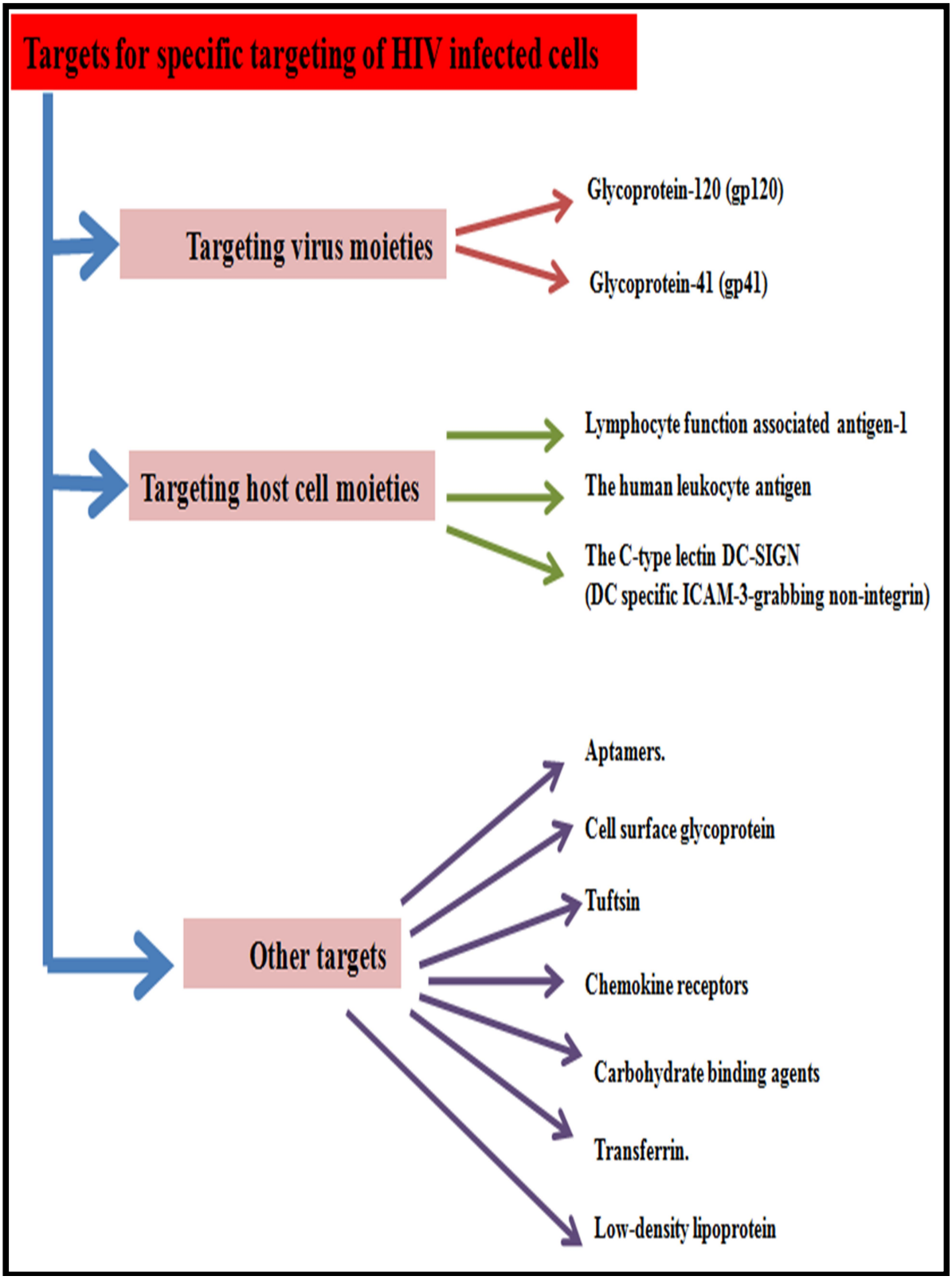

Figure 4: Targets for specific targeting of HIV infected cells

Table 1: Summarized details of Major classes of Antiretroviral agents

Major classes	Mechanisms	Antiretroviral agents
Nucleoside reverse transcriptase inhibitors (NRTI)	Active forms of these drugs are substrates for reverse transcriptase enzyme, and they result in termination of DNA chain elongation of the retrovirus.	They include zidovudine (AZT), didanosine (ddI), zalcitabine (ddC), stavudine (d4T), lamivudine (3TC), abacavir, tenofovir DF and emtricitabine
Protease inhibitors (PI),	They act primarily at the end of the HIV life cycle to cause the formation of non-infectious immature virions.	saquinavir, ritonavir, indinavir, nelfinavir, amprenavir, lopinavir (always used in combination with ritonavir), atazanavir, fosamprenavir
Non-nucleoside reverse transcriptase inhibitors (NNRTI)	These inactivate the HIV-1 reverse transcriptase enzyme by non-competitively binding directly to the HIV-1 reverse transcriptase structure likely at amino acid positions 100 and 103	nevirapine, delavirdine, efavirenz Etravirine, Rilpivirine
Peptide fusion inhibitors	These inhibit HIV from entering the target cells by hindering the gp41 protein on the virus	Enfuvirtide
Integrase inhibitors	Block the enzyme integrase and prevent the integration of the viral DNA into the host genome	Raltegravir, Dolutegravir
Entry inhibitors	Inhibit HIV-1 entry into healthy CD4+ cells	Maraviroc
Nucleotide reverse transcriptase inhibitors	upon phosphorylation to their respective active di/triphosphate nucleotide base analogue compete with the natural nucleotide bases during vRNA to vDNA strand synthesis by the reverse transcriptase polymerase	Tenofovir

Table 2: Traditional dosage forms and drugs imbedded in them

Dosage forms	Antiretroviral agents administered through this dosage forms
Tablet	Zidovudine Nevirapine Delavirdine Nelfinavir Fosamprenavir Zalcitabine
Capsule	Saquinavir Ritonavir Atazanavir Amprenavir Emtricitabine
Capsule film coated tablet	Efavirenz
Film coated tablet	Abacavir

Table 3: Biopharmaceutical considerations of Anti-retroviral drugs

Anti-retroviral drugs	Biopharmaceutical considerations
Zidovudine	loses considerable potency by the hepatic first pass metabolism
Didanosine	exhibits low intestinal permeability
NNRTIs	the oral bioavailability is limited due to their low aqueous solubility

Table 4: Novel Strategies designed antiretroviral drug delivery

Delivery of anti-HIV agents	By reducing frequency of dosing.
	Increasing bioavailability
	Decreasing degradation or metabolism in the gastrointestinal tract
	Improving the CNS penetration
	Targeted delivering of anti-HIV agents

Table 5: List of targeted novel carriers evaluated for HIV therapy.

Novel Approach	Drug	Features	Ref.
Liposome	Indinavir	Lesser toxicity and immunogenicity compared with free drug	18
Liposome	Zidovudine	Higher uptake of nano-formulation in spleen and lymph nodes	19
Liposome	Stavudine	Drug concentrated in the liver, spleen and lungs and lesser clearance of the system	20
Dendrimer	Lamivudine, Efavirenz	Increase uptake in liver, spleen, kidney macrophages	21

Table 6: Summary of Main Features & Limitations of other routes of Drug Delivery

Routes of Drug Delivery	Main Features	Limitations
Transdermal delivery	**The advantages offered by drug administration via the transdermal route include avoidance of first pass effect and/or GI degradation, reduced fluctuations in plasma drug concentrations, excellent targeting of the drug for local effect as well as improved patient compliance. The potential of ARVs for transdermal administration has therefore been extensively reported**	**limitations of transdermal delivery of drugs is poor skin/percutaneous penetration/absorption of drugs. Hence, the majority of ARV transdermal studies have focused on permeation enhancement investigating, inter alia, various chemical enhancers, types of vehicles (solvents/ co-solvents), as well as iontophoresis and anodal current application**
Buccal delivery	**Delivery of drugs via the buccal mucosa has received increased attention in the literature as an attractive alternative to the traditional oral and other conventional routes of drug administration. Use of the buccal mucosal route presents several advantages, such as the bypass of first pass hepatic metabolism and avoidance of gastrointestinal enzymatic degradation, thereby increasing the bioavailability of drugs; higher permeability than that of the other routes such as the skin; larger surface area for drug application, and good accessibility compared to other mucosal surfaces such as nasal, rectal and vaginal mucosa ARV drugs may therefore benefit from buccal mucosal administration instead of traditional oral administration**	**The buccal route for ARV permeation potential has not been comprehensively investigated. The reported studies to date have focused only on limited permeation enhancers, and no studies on the formulation and assessment of buccal delivery systems of ARVs could be found.**
Rectal delivery	**The rectal route has also been considered for effective delivery of ARV drugs that undergo first pass hepatic metabolism and/or extensive GI degradation.**	**The work in this area appears to be limited, most probably due to patient inconvenience, as well as to the fact that HIV/AIDS patients often suffer from diarrhoea.**

Table 7: Summary of Nano formulation approaches and their Features with specific drugs

Nano Approach	Drug	Features	Ref
Lipid nanoparticles	**Atazanavir and darunavir**	**Plasma drug concentrations persisted > 7 days (168 h)**	**22**
Lipid nanoparticles	**Lopinavir , Ritonavir and Tipranavir**	**50-fold higher PBMC concentrations, sustained for 7days**	**23**
Lipid-stabilized nano suspension (TLC-ART101)	**Lopinavir , Ritonavir and Tipranavir**	**Plasma and PBMC intracellular drug levels persisted > 2 weekst1/2 of TFV and LPV were 65.3and 476.9 h in plasma, and 169.1and 151.2 h in PBMCsTFV and LPV drug levels in LNMCs were up to 79-foldhigher than those in PBMCs at24 and 192 h**	**24**
Gold nano particles	**Raltegravir**	**Distribution in brain with 333.6ng Ag/g tissue**	**25**
Macrophageloadedpoloxamer-188/drug nano crystals	**Indinavir**	**Continuous drug release for 14days, could distribute to brain**	**26**
Lacto ferrin nano particles	**Efavirenz Lamivudine**	**>4-fold increase in AUC and AUMC, 30% increase in the Cmax, >2 fold in the t1/2 of each drug**	**27**
Folate acid-poloxamer 147nanocrystals	**Atazanavir Ritonavir**	**Drug bioavailability increased 5-fold, PD activity improved 100-fold**	**28**

SUMMARY AND CONCLUSION

- The main aim of drug targeting is to optimize a drug's therapeutic index by strictly localizing its pharmacological activity to the site or organ of action. The result of the targeting would be a significant reduction in drug toxicity, reduction of the drug dose, and increased treatment efficacy. Today, more therapeutic options are available and, even if remarkably more effective; the pharmacotherapy has become more complex making the need for effective DDS more crucial. The present section discusses the different approaches pursued to overcome the specific limitations shown by the different families of antiretro viral drugs.
- Based on the complexity of the disease and the formulation optimization and evaluation studies required, multidisciplinary research would be essential for eventual commercialization of Novel drug delivery systems containing antiretro viral drugs. Among the recent approaches of novel drug delivery system for anti-HIV drugs, targeted/intracellular drug delivery only in host cells capable of getting infected with HIV or more specifically HIV-infected cells and reservoirs holds great promise. The formulation design and optimization of analytical techniques requires multidisciplinary research for ultimate marketing of these novel drug delivery system products especially for antiretro viral drugs, because of the intricacy of the viral infections.
- The disputes related to antiretroviral drug therapy has been surmounted by adapting the various novel drug delivery methods, which pays pathway for many scientists to prove the efficiency of their techniques. Even though there are certain successful technologies emerging under this field, the progression of vesicular systems like liposomes and nanosized systems like nanoparticles exhibits superior attention and significance over the other schemes. Certainly, the present techniques with new therapeutic agents and scheduled regimens can provide noticeable improvement in the future of HIV infected people's living.
- The landscape of the HIV prevention and treatment field is constantly changing as new data emerge. As such the field needs to

be able to adapt to those needs. By investigating the characteristics that users will prefer, a dosage form with the highest acceptability can be designed. Traditional and Novel dosage forms offer several advantages over most dosage forms due to their low cost, ease of administration and adaptable formulation form. By designing Nano formulations for HIV/AIDS prevention and treatment instead of using classical forms, it is possible that Nanomerized formulation may represent a successful formulation worldwide.

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