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Approaches of Novel drug delivery systems for Anti-HIV agents

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Abstract:

The Human Immunodeficiency Virus (HIV) is a pandemic disease spreading very rapidly all over the world, causing approximately 15,000 or more new infections every day and the community acquiring sexually transmitted infections (STIs) is prone to easily acquire this HIV infections. The objective of the current review is to describe the comprehensiveness of the various advanced anti-HIV drug delivery systems and compounds that have been developed for targeting drugs to the macrophages, gastric mucosa and brain. 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. Several optional routes have been identified for the management of the ARV therapy which includes transdermal, mucosal (vaginal, rectal, buccal, etc.) and also lymphatic delivery, with the application of novel systems like nanoparticles, vesicular systems (liposomes, niosomes, ethosomes, emulsomes), micellar assemblies, etc. This review spotlights the prospectives of novel drug release systems used in preventing the transmission and treatment of retroviral infections.

Keywords: HIV, AIDS, Novel Technologies, Nanotechnology

Review Paper

Introduction

The acquired immune deficiency syndrome (AIDS) and associated infections caused by human immunodeficiency virus (HIV), has been identified as one among the dreadful ailment which pose alarming challenges to the community health throughout the world, especially more frightening in certain areas like sub-Saharan Africa.[1] The global level statistics have shown more than 33.2 million patients alive with this infection. Based on Indian health organization estimates India will have around 6-7 million HIV infected patients. 2.5 million people are newly infected (2007), 2.1 million as dead with AIDS (UNAIDS: http:// cmg.the body.com/unaids/2007), and 2.5 million in India, total HIV patients in India (2-3million/2006). Intervention like AIDS educational tools and counseling and ART the reason for transforming HIV infection from a fetal to a controllable chronic infectious disease. Presently, there are two known species of human immunodeficiency virus usually mentioned as HIV-1 and HIV-2 along with their sub-species, out of which HIV-1 infections are widespread around the world, whereas HIV-2 is highly prevailing in West Africa that takes longer duration to extend as immunodeficiency syndrome.

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. The GP-120 the protein present in the virus attaches with the two transmembrane receptors of the host cell, one is CD^{4+} receptor

and the other is either of the chemokine receptors namely CCR_5 or $CXCR_4$, or HIV macrophages or T-helper lymphocytes. T-Tropic viruses prefer the macrophage of the HIV-1 viruses in tropic types predominate in the brain.[3] The viral genome contains three structural genes - *gag, trol*, and *env* and six regulatory genes - *tat, rev, nef, vif, vpr* and *vpo*. With the help of these genes and other host cell resources, the viruses maximize its production. J.Cheinen *et.al*. has documented well about the immuno pathogenesis of HIV / AIDS from the early stage of disease till the end of the complete infection.[2] 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. The susceptible sites of the virus after infection are the central nervous system, lymph nodes, bone marrow, spleen, lungs, etc. out of which CNS is more prominent, that leads to remarkable damage or loss of neurons ultimately resulting in HIV related dementia, if untreated. The uncontrollable HIV-1 infection often ends with fatal results within 5 to10 years.[4]

The primary mechanism by which HIV transmission occurs is the direct contact of vaginal mucosal surface to the virus during sexual interaction. Pettfior *et.al* (http://www.rhruco.za/images/Docs/national%20survey%20RHRU.pdf) performed a reproductive health research study and found that a majority of the subjects (more than 93 %) were identified to use condom as successful preventive measures.

AIDS/ HIV DRUGS AND ITS LIMITATIONS

Infections with HIV remains as an incurable condition.[5] Existing system of classification of anti-retrovirals can be summarized as nucleoside reverse transcriptase inhibitor, nucleotide reverse transcriptase inhibitor, non- nucleoside reverse transcriptase inhibitor, protease inhibitor and the latest being fusion and integrase inhibitors.[6] The role of drugs categorized under various classes with its half life ($t_{1/2}$), bioavailability as well as available dosage forms are shown in table 1.[7]

The combination of these drugs are under prescription practice, which is indicated as highly active anti-retroviral therapy.[8] Between the new class of drugs under research is the assembly of budding inhibitors as well as the zinc finger inhibition along with HIV-1 capsid protein and human cyclophilin-A.[9] But, the main disadvantages of these drugs are extensive first pass metabolism and GIT degradation with short half life chiefly causing reduced and inconsistent bioavailability and poor targeting, and the development of multidrug resistance.[10] These molecules are also put up with certain physicochemical challenges starting from insolubility and leading to erratic formulation issues.[11]

The intention of this manuscript is to provide a combined and complete review of the diverse drug delivery models, both conventional and novel, that has been identified by various researchers as alternative routes for the application of new ARV drugs.

ADVANCED TECHNIQUES

Vaginal Creams and Gels

Even though a large number of semisolid formulations (ointments, creams, gels) are commercially available for the topical intra-vaginal drug delivery of microbicides, they are not patient reliable in most cases due to its

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unavoidable demerits such as greasy nature, leakage, inaccurate dose and poor spreading and circulation.[12] The recent research has focused remarkably on the improvement of controlled drug delivery through novel hydrogel systems.[13-15] The 93% alginate gel of nanoxynol-G has been fruitfully investigated for intra-vaginal spermicidal activity. A modification in the pH and osmolarity of the product showed a considerable difference in the diffusion and spermicidal activity of the drug. An innovative micro emulsion based gel formulation containing phenyl phosphate derivative of zidovudine was produced with superior and sustained anti-HIV effects.[16]

Vaginal Tablets and Suppositories

The large number of intra-vaginal delivery systems is also available in the form of tablets, pessaries and suppositories. The pessaries and suppositories with programmed time release mechanism are also been used as an alternative for the commercial vaginal tablets.[17]

Vaginal rings

A circular ring type delivery device containing two layers has been developed to insert into the vaginal cavity which release the drugs in a controlled rate. There are systems fabricated with a third layer (drug free - rate controlling elastomer membrane) which plays excellent role in minimizing the drug load and release. The fabrication of such device is merited with the usage and position control by the patient in a convenient manner to avoid interfering with coitus and also providing a continuous delivery of the drugs[18].

Bioadhesive intra-vaginal systems

To overcome the demerits of the conventional intra vaginal dosage forms such as poor retention, improper dose administration and leakage of the formulations, either new or fangled bioadhesive drug delivery systems are being launched in the market. The bio-adhesive polymers that have been used for intra-vaginal formulations includes polycarbophil, hydroxypropyl cellulose and polyacrylic acids. The first formulation worked on this principle was bio-adhesive tablets of Bleomycin for the treatment of cancer.[19,20] There are systems used for delivering microbicides using mucoadhesive microparticulate vaginal systems which shall be multi-phase liquid or semisolid that have been designed as not to slip from the vagina.[21,22]

Sustained release dosage forms and Ceramic implants

Sustained release delivery systems are developed to attain a constant release of drugs at predictable and reproducible kinetics and the model drug which have been formulated as sustained release formulation is Didanosine (ddI) The survey of literatures have shown a tremendous scope in drug delivery utilizing the ceramic implants to alter the release pattern for anti retroviral drugs such as deoxynucleoside.[23]

Liposomes and ethosomes

Liposomes are vesicular systems made up of phospholipids and cholesterol used for drug delivery of both water soluble and oil soluble drugs. The same was used for the delivery of Azidothymidine (AZT) and studied using mice model. The results found that there is no bone marrow toxicity of AZT encapsulated in liposomes compared to free drug[24]. The didinosin encapsulated for the enhancement of half life and achieved the half-life of 24 hrs from 3-4 hrs[25], and the liposomes shows better cell uptake and anti-hive activity in monocytes macrophages and HIV-1 infected macrophages than free didinasin.[26,27] The ethosomes a kind of vesicular system containing high composition of

phospholipids and alcohols also used for the delivery of anti-HIV drugs and found better effect over liposomes.[28]

Emulsomes

A novel type of lipoidal vesicular system, emulsomes consisting of an internal solid fat core surrounded by a phospholipid bilayer, was identified for the targeted delivery of anti-retroviral drugs. Using rat models, an enhanced uptake of this formulation by the liver cells was also demonstrated. The intracellular liver targeting was found to be tremendously potential for the cation based emulsome system.

Micelles and Microemulsions

The anti-retroviral molecules with decreased bioavailability and increased entero hepatic metabolism were successfully bypassed from the portal blood to the HIV rich intestinal lymph circulation through the novel microemulsion type of formulation approach, which could ultimately result in its enhanced bioavailability. Using oleic acid, three different microemulsions were formulated and studied in rat models for targeted intestinal lymphatic transport mechanism.[29] The microemulsions resulted in greater mesenteric lymph levels compared to the micellar formulation of cremophore-oleic acid mixed micelles, D-alpha tocopheryl PEG1000 succinate and oleic acid mixed micelles.

Suspensions

Pharmaceutical nanosuspensions are finely dispersed solid dry particles in an aqueous vehicle for either oral or topical use for parenteral and pulmonary administration, which are made up of sterile or non-toxic, biodegradable or non-biodegradable polymer. The suspension formulated with lipid related complexes for subcutaneous administration have been reported with enhanced localization in lymphoid tissue and also reduces viral load, in the HIV-2287 diseased macrophages.[30] The concentration in peripheral region and the visceral lymph nodes was in the range of 2250-2270%, that was higher compared to placebo as <35% lipid free drug given in individuals. This lipid complex of drug reduced the viral load and increased the CD4 T-cell count.

Transdermal

Transdermal system has created an influence, because this system gives the substantial advantage of a non parenteral route for drug administration, avoidance of first pass metabolism (gut and hepatic as well), GI degradation, decreased side effects by reducing fluctuation in plasma, and excellent targeting of drug for improved patient compliance.[31] The most challenging issue and drawback with transdermal route of absorption is the uncertain and low cutaneous transport for the uptake of molecules. Majority of the studies involved in the enhancement of penetration of drugs with the help of salt formation, solvent and co-solvent addition, iontophoresis or anodal current application, by which litho simple or combination helps to enhance the permeation of ARV drugs. The transdermal gels and patches have been developed for AZT [32,33] in addition with polymeric ingredients like gum matrix.[34] Different *in-vivo* and *ex-vivo* studies conducted on ARV drugs like ddI, ddC and AZT using animal's skin like rat, mouse, pig and human cadaver have proved the efficacy of these ARV drugs via the transdermal route.

Buccal delivery

Buccal delivery of drugs can bypass the enterohepatic circulation and neglect gastro intestinal degradation, which striked many researchers to choose it over the traditional oral and conventional routes for providing superior

bioavailability of drugs.[35] It shows greater transmembrane penetration compared to skin drug administration and also provides several advantages over other mucosal routes of delivery like nasal, rectal and vaginal mucosa, which includes its larger surface area, easy accessibility for application, enormous capillary blood supply. The ARV drugs are highly benefited through buccal mucosal drug delivery as preferable choice. Shojaei *et. al* used ddC as model drug and investigated by using the safe and effective permeation enhancer method through buccal route. In this study 1-menthol shows increase in permeation of ddC with enhancement factor of 2.02 and t ½ of 6 hrs. It was proved that its not concentration dependant, by varying the concentration as 0.1, 0.2 and 0.3 mg/ml of 1-menthol.[36] In other study, it was found that the basal lamina present within the buccal mucosal epithelial layer work as the essential membrane wall for the penetration of ddC. As well, they concluded the SGC (sodium glycodeoxy cholate) enhancing anti-retroviral drug therapy.

Rectal delivery

Rectal administration of drugs has been recognized as successful eternal route for such drugs, exhibiting high enterohepatic metabolic reaction and gastro intestinal decomposition. Sustained release AZT HPC suppositories were assessed in rats.[37] Suppositories of AZT in the dose range of 10 mg/kg maintain constant plasma concentration above 1mg/kg for more than 6 hrs. Certain research works have also reported highlighted results with AZT suppository delivery systems. Also studies revealed that the absorption data and other pharmacokinetic parameters similar to sustained release device could be achieved by rectal administration of AZT. [38]

Nano-containers

The concept of ARV targeting using the carriers like dendrimers based systems has also been explored well. Dendrimers are macromolecules synthetically designed as spherical and highly branched structures. These macromolecules have come out into the sight as thrived tool among the existing drug carriers for targeted delivery, due to their uniqueness in structural design.[39] Hence, predictably they have been identified initially for targeting of anti-retroviral drugs. The poly (propylene imine) dendrimer based nanocontainers for targeting Efavirenz (EFV) to Mo/Mac.[40] These molecules are referred as nanocontainers since they behave like closed nanosize vessel with entrapped drug inside. Moreover, the mannosylated PPi dendrimers have been declared as a valuable carrier system for site specific delivery of anti-retroviral drug like EFV.

Nanopowder

Nanopowders have been utilized efficiently through peroral route of drug delivery for the augmentation of solubility and drug release rate of many hydrophobic drugs.[41] When Loviridine nanopowder morphology was analyzed, plate resembling features were observed whereas the untreated substance show crystal structures.

Nanoparticles

Nanoparticles can exist as either solid colloidal particles or suspended in liquid media, the particles being in the size range of 1-100 nm. Depending on the polymer type and ratio in the formulation designed, the size of these particles can be varied and effectively launched for site specific and sustained release of drugs.[42] This concept works better with molecules showing poor physicochemical strategies like insolubility and instability. When these nanoparticles were treated with macrophages secluded from HIV infected people, their uptake was superior than

pure drug. In the same way, when Saquinavir and DDC nanoparticles were formulated using poly (hexacyanoacrylate) [43] through emulsion polymerization technique, a drastically greater efficiency was seen for the nanoparticles than the pure drug suspension. An *in-vivo* study in rats to investigate the oral delivery of AZT bound to hexacyanoacrylate nanoparticles for delivery for the reticuloendothelial cells, by Loberberg, Ananjo and Kruter.[44] In a latest in-vitro study, the uptake of AZT nanoparticles by pronuclear leukocytes was demonstrated, in which the effect of the nanoparticles prepared with poly (lactic acid) poly (ethylene glycol) polymer was found to be reliant based on PEG ratio. Whereas the nano systems get easy access to the brain through the mechanism of endocytosis, which can also move away from the locality of efflux pumps.[45]

The polymeric systems identified for enhanced permeability effects of the various drugs are all being reported with smaller particle size.[46] Ligand based nanoparticles have also emerged out for receptor mediated targeting approach of ARV drugs. Certain approaches were also utilized for targeting other sites such as GI mucosa and its inter connected lymph tissues. Apart from targeting approach, the ARV nanoparticles were paid attention for formulation modification to boost up the drug loading and reduce the systemic toxicity and also raise its absorption rate, as like facilitated pH sensitive drug release.[47,48]

Table 1: Approved Antiretroviral Drugs for the Treatment of HIV Infection including its date of approval, half life and available dosage forms

Drugs	Approved date	Half- lives (in Hrs)	Dosage form
Entry inhibitors			
Maraviroc (UK-427,857, Selzentry®)	06 Aug 2007	14-18	Tablet
Fusion inhibitors			
Enfuvirtide (T20, Fuzeon®)	13 Mar 2003	3.8	Powder for SC Injection
Integrase inhibitors			
Raltegravir (MK-0518, Isentress®)	12 Oct 2007	9	Tablet
Reverse transcriptase inhibitors			
Nucleoside/nucleotide analogues			
Abacavir (ABC, Ziagen®)	17 Dec 1998	1-2	Tablet, liquid
Didanonise (ddI, Videx®)	09 Oct 1991	1.3-1.6	Tablet, Capsule, solution
Emtricitabine (FTC, Emtriva®)	02 July 2003	10	Capsule
Stavudine (d4T, Zerit®)	24 June 1994	1-1.6	Tablet, Powder
Lamivudine (3TC, Epivir®)	17 Nov 1995	3-6	Tablet, liquid
Tenofovir (DF, Viread®)	26 Oct 2001	17	Tablet
Zalcitabine (ddC, Hivid®)	19 June 1992	1-3	Tablet
Zidovudine (AZT, Retrovir®)	19 Mar 1987	1.1	Capsule, liquid
Non-nucleoside inhibitors			
Delavirdine (DLV, Rescriptor®)	4 Apr 1997	5.8	Tablet
Efavirenz (EFV, Sustiva®)	17 Sep 1998	40-50	Tablet, capsule, solution
Etravirine (TMC125, Intelence®)	18 Jan 2008	30-40	Tablet
Nevirapine (NVP, Viramune®)	21 June 1996	25-30	Tablet, syrup
Protease inhibitors			
Amprenavir (AMP, Agenerase®)	15 Apr 1999	7-10	Capsule, solution
Atazanavir (ATZ, Reyataz®)	20 June 2003	7	Capsule
Darunavir (TMC-114, Prezista®)	23 June 2006	15	Tablet
Fosamprenavir (GW-433908, Lexiva®)	20 Oct 2003	7.7	Tablet, capsule
Indinavir (IDV, Crixivan®)	13 Mar 1996	1.2-2	Capsule
Lopinavir (ABT-378, Kaletra®)	15 Sep 2000	5-6	Tablet, capsule
Nelfinavir (NFV, Viracept®)	14 Mar 1997	3.5-5	Tablet, powder
Ritonavir (RTV, Norvir®)	01 Mar 1996	3-5	Tablet, capsule, liquid
Saquinavir (SQV, Fortovase®, Invirase®)	07 Nov 1997	1.5-2	Tablet, Capsule
Tipranavir (TPV, Aptivus®)	22 June 2005	5-6	Capsule

Conclusion

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. The formulation design and optimization of analytical techniques requires multidisciplinary research for ultimate marketing of these NDDS products especially for ARV drugs, because of the intricacy of the viral infections. Certainly, the present techniques with new therapeutic agents and scheduled regimens can provide noticeable improvement in the future of HIV infected people's living.

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