Review Article

A Review on Novel Drug Delivery Systems for Design of Formulations of Antiviral Drugs

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ABSTRACT

The global impact of viral infections and emergence of new viruses challenges drug discovery and formulation development. However, in an attempt to provide ready reference in this present pandemic situation, this article presents review on novel drug delivery systems that bypass the short comings related to conventional treatment and could permit the delivery of anti-viral drugs to specific target sites and viral reservoirs in the body for effective treatment of viral hazard.

Keywords: New viruses, challenges, Antiviral drugs, Novel drug delivery systems.

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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 anti-viral 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].

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[2-6]

Drug 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 reduces the activity.	• Nevirapine – 25- 30 hrs • Rilpivirine – 50 hrs • Etravirine – 30-40 hrs • Doravirine – 15 hrs • 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
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
Post attachment inhibitors	• Prevents HIV from entering certain immune cells.	• Ibalizumab – 40-50 hrs
Chemokinetic coreceptor antagonists	• Maraviroc binds to the host cell CCR5 receptor to block binding of viral gp120. • Maraviroc is the only approved antiretroviral drug that targets a host protein.	• Maraviroc – 16 hrs
Multi-class combination products	• Combine multiple medications into 1 drug form	• Lopinavir and ritonavir (Kaletra) • Atazanavir and cobicistat (Evotaz) • Lamivudine, Abacavir, Zidovudine (Trizivir)

Novel Drug Delivery Systems

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.

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 efficiency[7,8,9]. 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[10,11].

S. 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.

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 time[12-14]. They also have advantages like limiting the fluctuations within the therapeutic range and incorporating drug into the system without any chemical reaction[15.16,17].

S. No	Drug	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.

Antiretroviral targeting can be done by using carriers like dendrimer-based systems. Dendrimers are macromolecules synthetically designed as spherical and branched structures. They gain attention due to their uniqueness in the structural design from existing drug carriers used for targeted delivery[18]. The drug was entrapped inside the closed nanosized dendrimers. Mannosylated PPi dendrimers were declared as a valuable carrier system for site specific delivery of antiretroviral drug like Efavirenz.

S. No	Drug	Findings
1	Efavirenz	Efavirenz loaded tuftsin conjugated fifth generation Poly (propylene eimine) dendrimers showed 49.31% entrapment efficiency and was found to reduce viral load by 99% at a concentration of 0.625 ng/ml.

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[23,24,25,26].

Nano-Carriers

S. No	Drug	Findings
1	Efavirenz	Efavirenz loaded solid lipid nanoparticles formulated by solvent emulsification shows 83.75% drug release in 48 hours.
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	Lamivudine	Lamivudine loaded polymethyacrylic acid nanoparticles formulated by nanoprecipitation method shows sustained release for 24 hours.
6	Abacavir	Abacavir sulphate loaded albumin nanoparticles formulated by desolvation method. The in vitro drug release for 24 hours was found to be 51.36%
7	Zidovudine	Zidovudine loaded chitosan nanoparticles formulated emulsion droplet coalescence method shows 75.89% drug release for 24 hours.
8	Stavudine	Stavudine loaded chitosan nanoparticles were formulated. In vitro release studies showed 93% drug release in 24 hours.

Niosomes

Niosomes are non-ionic surfactant vesicles obtained by admixture of non-ionic surfactant and cholesterol with hydration in aqueous media[27,28]. 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[29,30,31].

S. No	Drug	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.

Sustained and Controlled Release Systems by Oral Route

The most common route of administration for drug delivery into the body is oral route of administration due to its flexibility and patient compliance. Conventional tablet dosage forms are generally associated with some limitations such as frequent administration, drug fluctuations, poor bioavailability and toxic side effects[32-35]. To overcome these drawbacks of conventional oral dosage forms, controlled and sustained release formulations have been developed to improve overall therapeutic benefits of anti-HIV drugs and to achieve effective therapy. Extended-release tablets, sustained release tablets, bilayer tablets, floating tablets, bio adhesive tablets comes under controlled release formulations. The main advantages are reduced frequency dosing, improved therapeutic efficacy and avoid side effects related to conventional tablets. Retrovir, Epivir, Ziagen, Viread are some oral controlled release formulations for antiretroviral drugs available in the market[36-40].

S. No	Drug	Controlled release system	Polymers	Method	Findings
1	Acyclovir	Matrix tablets	HPMC K 100 Locust bean gum, Xanthan gum, Tamarind seed polysaccharide	Direct compression	Controlled drug release over 12 hours, Diffusion controlled drug release followed zero order kinetics.
2	Abacavir	Sustained release tablets	Guar gum, Xanthan gum, Eudragit L 100	Direct compression	Prolonged release up to 24 hours and follows zero order kinetics
3	Lamivudine	Matrix tablets	Eudragit RS 100, Eudragit RL 100, Microcrystalline cellulose	Direct compression	Drug release was slow and spread over 24 hours
4	Nevirapine	Matrix tablets	HPMC K4M, HPMC K15M	Wet granulation	Prolonged drug release and improved bioavailability
5	Ritonavir	Sustained release tablets	HPMC K100M, Eudragit RS 100, Chitosan	Wet granulation	Drug release was sustained for a period of 12 hours and followed mixed order kinetics
6	Stavudine	Matrix tablets	Eudragit RL 100, Ethyl cellulose	Direct compression	Controlled release up to 12 hours and followed zero order kinetics.
7	Zidovudine	Matrix tablets	Eudragit RS 100, Eudragit RL 100, Ethyl cellulose	Direct compression	Controlled release for prolonged period of time and follows zero order.
8	Acyclovir	Floating tablets	Polyvinyl pyrrolidone, polyvinyl alcohol, HPMC	Wet granulation	Floating time is in the range of 20-24 hours. Followed zero order kinetics.

Emulsomes

Emulsomes are lipoidal vesicular system consisting of an internal solid fat core surrounded by a phospholipid bilayer. They have hydrophobic load inside the solid core and within the bilayers. The key feature of Emulsomes is that the fat core is in the bulk in a solid or liquid crystalline phase rather than existing as oil in a liquid phase which discriminates emulsomes from emulsions and allows encapsulation of higher amounts of lipophilic compounds. Emulsomes helps for targeted delivery of antiretroviral drugs[41, 42].

Implants

Implants sanction long-acting parenteral delivery of antiretroviral drugs and able to allow protective drug concentrations for a year or longer with a single implant. Implants require special procedures for insertion and removal. They are economical, scalable to manufacture, well tolerated, can remain in place for upto 5 years, more consistent and shows predictable drug release kinetics. Biodegradable implants are also present. Antiretroviral drugs are most suitable for implant formulation and delivery with exceptionally high antiviral potency. Investigational implants containing tenofovir alafenamide,

Nevirapine, entecavir have been developed and tested in animal models[43,44].

Due to the adverse effects of AZT associated with oral and intravenous administration, attempts have been made to use ceramic implants to modulate the release of antiretroviral drugs. In attempt to that studies carried out on ceramic thymidine, the normal counterpart of azidothymidine (AZT), by means of alumino-calcium-phosphorous oxide (ALCAP) ceramic implantable capsules in rats and results showed the sustained release of drug for 120 days. This subsequently concluded that these could be considered for the delivery of AZT.

Potential advantages and disadvantages of antiretroviral implants as compared to injectables.

Advantages	Disadvantages
Implants can remain in place for years	Implants can migrate from original insertion site to place where palpation is difficult.
Pharmacokinetic properties may not depend on injection site	Minor surgical procedure is required to remove
Avoid high injection volumes	Must be removed at the end of product life span.

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.

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