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.

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 take the 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.

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.

<table>
<thead>
<tr>
<th>Drug Class</th>
<th>Brief Notes</th>
<th>Drug and Their Half -life (hr)</th>
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<tbody>
<tr>
<td>Integrase inhibitors</td>
<td>• Integrase is viral enzyme that infect T cells by putting HIV DNA into human DNA. &lt;br&gt; • Integrase inhibitors stop the action of integrase &lt;br&gt; • Raltegravir was first FDA approved integrase inhibitor.</td>
<td>• Dolutegravir – 14 hrs &lt;br&gt; • Elvitegravir – 12.9 hrs &lt;br&gt; • Raltegravir – 9 hrs &lt;br&gt; • Bictegravir – 18 hrs</td>
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<td>Protease inhibitors (PI)</td>
<td>• HIV needs protease to replicate in the body. &lt;br&gt; • When protease cannot do its job, the virus can’t complete the process that make new copies. &lt;br&gt; • Hence, protease inhibitors reduce the number of viruses that can infect more cells.</td>
<td>• Atazanavir – 7 hrs &lt;br&gt; • Darunavir – 15 hrs &lt;br&gt; • Lopinavir – 6.9 hrs &lt;br&gt; • Indinavir – 1.2-2 hrs &lt;br&gt; • Saquinavir – 1.5-2 hrs &lt;br&gt; • Tipranavir – 5.5-6 hrs</td>
</tr>
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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. 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 they have limited hydrophilic drug loading capacity, short shelf life, cost, poor scale up.

**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. They also have advantages like limiting the fluctuations within the therapeutic range and incorporating drug into the system without any chemical reaction.

<table>
<thead>
<tr>
<th>S. No</th>
<th>Drug</th>
<th>Findings</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Zidovudine</td>
<td>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.</td>
</tr>
<tr>
<td>2</td>
<td>Nevirapine</td>
<td>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.</td>
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<tr>
<td>S. No</td>
<td>Drug</td>
<td>Findings</td>
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<tr>
<td>-------</td>
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</tr>
<tr>
<td>1</td>
<td>Lamivudine Chitosan with Lamivudine microspheres prepared using ionic gelation method showed 23.32-68.72% invitro drug release.</td>
<td></td>
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<tr>
<td>2</td>
<td>Zidovudine Ethyl cellulose and zidovudine microspheres using dry-in-oil method, good bio adhesive property was observed by invitro release.</td>
<td></td>
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<tr>
<td>3</td>
<td>Stavudine Eudragit RS100 using Stavudine microspheres by emulsion solvent evaporation method showed 88% entrapment efficiency and buoyant for more than 12 hours.</td>
<td></td>
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<tr>
<td>4</td>
<td>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.</td>
<td></td>
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<tr>
<td>5</td>
<td>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.</td>
<td></td>
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**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. 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.

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<td>1</td>
<td>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.</td>
<td></td>
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**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.
Emulsomes helps for targeted delivery of antiretroviral encapsulation of higher amounts of lipophilic compounds. Emulsomes discriminate emulsomes from emulsions and allows encapsulation of higher amounts of lipophilic compounds. Emulsomes helps for targeted delivery of antiretroviral drugs41, 42.

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 effects32-38. 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 come under controlled release formulations. The main advantages are reduced frequency dosing, improved therapeutic efficacy and avoid side effects related to conventional tablets. Retrovir, Epivir, Zidagram, Viread are some oral controlled release formulations for antiretroviral drugs available in the market36-40.

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 drugs41, 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\textsuperscript{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.

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

**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.

**REFERENCES**


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