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RECENT RESEARCH ON CONTROLLED RELEASE OF ANTI RETROVIRAL DRUGS: A REVIEW

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ABSTRACT

Antiretroviral drugs are active against human immunodeficiency virus (HIV) which is a retrovirus. They are useful in prolonging and improving the quality of life and postponing complications of acquired immunodeficiency syndrome (AIDS) or AIDS related complex (ARC), but do not cure the infection. Over the past 20 years, more than 20 drugs have been introduced and a large number of others are under development. Controlled release formulation is needed for several antiretroviral drugs to enhance their therapeutic efficacy and patient compliance. Anti retroviral drugs and recent research on controlled release of anti retro viral drugs are reviewed in this article.

KEYWORDS: Anti retroviral drugs, Controlled release, Recent research.

INTRODUCTION

The last 40 years have seen the development of several antiviral drugs with therapeutic value in treating life-threatening or debilitating diseases such as those caused by HIV, hepatitis B virus, herpes viruses (such as herpes simplex virus and varicella zoster virus) and influenza virus. These developments are due to technical breakthroughs in the cultivation of viruses in the laboratory, identification of viral enzymes and, more recently, their molecular biology. Antiretroviral drugs[1] are active against human immunodeficiency virus (HIV) which is a retrovirus. They are useful in prolonging and improving the quality of life and postponing complications of acquired immunodeficiency syndrome (AIDS) or AIDS related complex (ARC), but do not cure the infection. The clinical efficacy of antiretrovirus drugs is monitored primarily by plasma HIV-RNA assays and CD4 lymphocytes count carried out at regular intervals.

The first antiretroviral (ARV) drug, zidovudine was developed in 1987.Over the past 20 years, more than 20 drugs belonging to the following three classes have been introduced and a large number of others are under development.

Nucleoside reverse transcriptase inhibitors (NRITS)

Zidovudine: It is a thymidine analogue (azidothymidine, AZT), the prototype NRTI. After phosphorylation in the host cell, zidovudine triphosphate selectively inhibits viral reverse transcriptase (RNA-dependent polymerase) in preference to cellular DNA polymerase.

Didanosine (ddi): It is a purine nucleoside analogue which after intercellular conversion to didanosine triphosphate competes with ATP for incorporation in viral DNA, inhibits HIV reverse transcriptase and terminates proviral DNA.

Stavudine (d4T): It is also a thymidine analogue which acts in same way as AZT. The anti + - HIV efficacy of stavudine is comparable to AZT, and it is used in combination regimens.

Lamivudine (3TC): This deoxycytidine analogue is phosphorylated intracellularly and inhibits HIV reverse transcriptase as well as hepatitis B virus (HBV) DNA polymerase. Its incorporation into DNA results in chain termination. Lamivudine is used in combination with other anti-HIV drugs, and appears to be as effective as AZT. It is also frequently used for chronic hepatitis B.

Abacavir (ABC): This guanosine analogue is a potent ARV drug that acts after intracellular conversion to carbovir triphosphate. Resistance to ABC develops slowly, and it exhibits little cross resistance with others NRTIs.

Non-nucleoside reverse transcriptase inhibitors (NNRTIS)

Nevirapine (NVP) and Efavirenz (EFZ): These are nucleoside unrelated compounds which directly inhibit HIV reverse transcriptase without the need for intercellular phosphorylation. They are more potent then AZT on HIV -1, but do not inhibit HIV -2. The NNRTIs are indicated in combination regimens for HIV, and have succeeded in reducing HIV-RNA levels when an earlier regimen has failed.

Retroviral protease inhibitors (PIs)

An aspectic protease enzyme encoded by HIV is involved in the production of structural proteins and enzymes (including reverse transecriptase) of the virus. The large polyprotein is

broken into various functional components by this enzyme. This protease acts at a late step in HIV replication, i.e. maturation of the new virus particles when RNA genome acquires the core proteins and enzymes. Five protease inhibitors-Indinavir (IDV), Nelfinavir (NFV), Saquinavir (SQV), Ritonavir (RTV), Lopinavir (in combination with ritonavir LPV/r) have been marketed in india for use against HIV. They bind to the protease molecule with its cleaving function, and more effective viral inhibitors than AZT.

Anti-Herpes virus drugs

Acyclovir: This deoxiguanosine analogue antiviral drug requires a virus specific enzyme for conversion to the active metabolite that inhibits DNA synthesis and viral replication. Only about 20% of an oral dose of acyclovir is absorbed. Plasma $t_{1/2}$ is 2-3 hours. Renal impairment necessitates dose reduction.

Controlled Release of Anti retroviral Drugs

The following anti retroviral drugs are formulated as oral sustained release or controlled release products for the reasons given under each.

Lamivudine

It is a potent antiviral agent used in the treatment of AIDS. Conventional oral formulation of lamivudine are administered multiple times a day (150mg twice daily) because of its moderate biological half-life ($t_{1/2}$) of 5-7h.[2-3] Treatment of AIDS using conventional formulations of lamivudine is found to have many drawbacks, such as adverse side effects resulting from accumulation of drug in multidose therapy,[4] poor patient compliance, and high cost. Sustained release once-daily formulation of lamivudine can overcome some of these problems.

Abacavir

It is an antiviral drug used in the treatment of human deficiency virus (HIV). The half-life of this drug is 1.54 ± 0.63 hours and this necessitates its administration in controlled release formulations.[5]

Acyclovir

It is a potent antiviral drug useful in the treatment of Herpes simplex, Herpes zoster, Chicken pox and HIV infection. Acyclovir has a short biological half life 2.5h and also dosing frequency of 200mg/400mg 5 times a day depending upon type of infection. An alternative

dose of 800mg leads to plasma fluctuations. Controlled release formulation is needed for acyclovir because of it short biological half life and also to overcome adverse side effects, poor patient compliance, reduce dose and maintain uniform drug levels.[6]

Nevirapine

It is a non-nucleoside reverse transcriptase inhibitor (NNRTI) of human immuno-deficiency virus type1 (HIV-1), block polymerase activity after binding directly to the HIV-1 reverse transcriptase leading to disruption of the enzyme's catalytic site.[7] Anti retroviral therapy with nevirapine has demonstrated significant activity in HIV infected patients in combination drug with highly active anti retroviral therapy. Nevirapine is weak base with low water solubility, and belongs to BCS class II drug. In human, NVP is well absorbed orally with an estimated absolute bioavailability of about 90%. Generally NVP immediate release 200mg tablets are taken twice a day. A Nevirapine sustained release (NVP SR) once daily tablet formulation could be used to maintain optimum peak plasma concentration for effective viral suppression.

Ritonavir

Ritonavir is the most commonly used antiretroviral drug in treatment of AIDS and HBV infections. Its half life is about 3-5 h and is administered in dose of 300mg thrice a day. Sustained release formulations are needed for ritonavir to reduce dosage frequency and to achieve constant plasma drug levels.[8]

Stavudine

It is the Food and Drug Administration approved drug for clinical use in the treatment of HIV infection, acquired immune deficiency syndrome (AIDS) either alone or in combination with other antiviral agents. The drug has a very short half life (1.30 hrs). However, patients receiving Stavudine develop neuropathy and lactic acidosis. The side effects of Stavudine are dose dependent and a reduction of the total administered dose reduces the severity of the toxicity.[9] To reduce the frequency of administration and to improve patient compliance, a once daily sustained release formulation of Stavudine is desirable. Converting twice daily regimen of Stavudine into once daily improve adherence and, therefore enhances the effectiveness of antiretroviral therapy.[10]

Zidovudine

Zidovudine is the first anti-HIV compound approved for clinical use is widely used for treatment of AIDS either alone or in combination with other antiviral agents. However, the main limitations to therapeutic effectiveness of zidovudine are its dose-dependent haematological toxicity, low therapeutic index, short biological half-life, and poor bioavailability.[11] The biological half-life of zidovudine is 4 h, thus necessitating frequent administration (3 to 4 times a day) to maintain constant therapeutic drug levels. Treatment of AIDS using conventional formulations of zidovudine is found to have many drawbacks such as adverse side effects due to accumulation of drug in multi-dose therapy,[12-13] poor patient compliance[14] and high cost. Sustained release formulations of zidovudine can overcome some of these problems.

Recent Research on Controlled Release of Antiretroviral Drugs

Several studies reported in recent years on controlled release of antiretroviral drugs. These studies are summarised in Table 1.

Table 1: Summary of Recent Research on Controlled Release of Antiretroviral Drugs

S. No	Drug name	Controlled release system	Polymers used	Method	Significant Result	Ref.
01	Acyclovir	Matrix tablets	Carbopol 934P, MCC PH 102, HPMC K15M.	Direct compression	Drug release was sustained over 10h and followed zero order kinetics.	[15]
02	Acyclovir	Matrix tablets	HPMC K100M, Locust bean gum, Xanthan gum, Tamarind seed polysaccharide.	Direct compression	Controlled drug release over 12 h; release was diffusion controlled, followed zero order kinetics	[16]
03	Acyclovir	Matrix tablets	Guar Gum	wet granulation	Increase in the concentration of Guar gum retarded the drug release rate upto 12h.	[17]
04	Acyclovir	Matrix tablets	HPMC K100M, Locust bean gum, Karaya gum.	Direct compression	Controlled release of acyclovir is depended on polymer combination and	[18]

					concentrations. Release was by non-fickian diffusion.	
05	Acyclovir	Floating Tablets	HPMC K15M and Polyethylene oxide (Polyox WSR 303)	Direct compression	Increased gastric residence time and controlled release up to 12h.	[19]
06	Acyclovir	Floating Tablets	Polyvinyl pyrrolidon , Polyvinyl alcohol and HPMC	Wet granulation	Floating time is in the range of 20-24 h, followed zero order kinetics.	[20]
07	Acyclovir	Floating Tablets	HPMC K4M, Compritol 888 ATO,	Direct compression	Prolonged gastric residence time and enhanced therapeutic effect.	[21]
08	Acyclovir	Sustained release tablets	Xanthan gum, MCC, Sodium alginate and HPMC K15M	Direct compression	Controlled drug release for a period of 12h from optimised formulation. Release followed zero order kinetics	[22]
09	Acyclovir	Matrix Tablets	Tamarind kernel powder, Polyvinyl pyrrolidone,	Wet granulation	Tablets fulfilled all the requirements for sustained release tablets	[23]
10	Acyclovir	Floating Matrix Tablets	HPMC K 100 M , HOMC K 15 M	Direct compression	Prolonged gastric residence time and sustained release over 12h.	[24]
11	Acyclovir	Muco-adhesive tablets	Carbopol-934P , HPMC K 100 M	Direct compression	Prolonged drug release and increased bioavailability	[25]
12	Acyclovir	Floating matrix tablets	HPMC K15M, K4M, Guar gum , Sodium	Direct compression	Drug release was sustained upto 16h and followed zero order kinetics.	[26]
13	Acyclovir	Floating matrix tablets	HPMC and Xanthum gum	Direct compression	Increased gastric residence time and enhanced bioavailability	[27]
14	Acyclovir	Matrix Tablets	Carbopol 97 , PVPK30	Direct compression	Prolonged sustained release, good swelling and mucoadhesion	[28]

					properties. Drug release by non-fickian diffusion.	
15	Acyclovir	Mucoadhesive tablets	PLGA , PluronicF68, Polycorbophil.	Solvent deposion, Direct compression	Mucoadhesion is dependent up on the polymer ratio, drug release was by non-fickian diffusion.	[29]
16	Abacavir	Sustained Release Tablets	Guar Gum, Xanthum Gum, Eudragit L100	Direct compression	Prolonged release upto 24h.Release followed zero order kinetics	[30]
17	Abacavir	Nanoparticles	Biodegradable polymers	In situ nano emulsion	Sustained release up to 16h and followed zero order kinetics	[31]
18	Lamivudine	Matrix tablets	HPMC K100M	Direct compression	Drug release was sustained up to 20h and followed non fickian diffusion	[32]
19	Lamivudine	Extended release floating tablets	HPMC K4M, HPMC K15M , HPMC K100M.	Direct compression	Increased gastric residence time, prolonged drug release and decreased dose frequency	[33]
20	Lamivudine	Matrix tablets	HPMC K4M, HPMC K15M , HPMC K100M, Povidone K30.	Wet granulation	Drug release from the tablets was slow and spread over within 24h. Release was by non- fickian diffusion	[34]
21	Lamivudine	Matrix tablets	Methocel K15M	wet granulation	Sustained release over 8h. Release was by fickian diffusion	[35]
22	Lamivudine	Matrix tablets	Cellulose ethers, Xanthan gum, Locust bean gum, Guar gum	Direct compression	The drug release was extended over a period of 24 hours with zero order release mechanism	[36]
23	Lamivudine	Matrix tablets	Eudragit RS100, Eudragit RL 100, Microcrystalline	Direct compression	Drug release was slow and spread over 24h	[37]

			cellulose.			
24	Nevirapine	sustained release tablets	HPMC K4M, K100M, xanthan gum, Tragacanth.	Wet granulation	Sustained release up to 12 h, improved bioavailability and patient compliance	[38]
25	Nevirapine	Matrix tablets	HPMC K4M and K15M	Wet granulation	Prolonged drug release and improved bioavilability	[39]
26	Ritonavir	Sustained release tablets	HPMC K100M, Eudragit RS 100, Chitosan	Wet granulation	Drug release was sustained up to 12h and followed mixed order kinetics.	[40]
27	Ritonavir	Microspheres	HPMC,Sodium bicarbonate, Calcium cloride	Ion gelation	Controlled release was depended upon concentration of polymers used. Release was by non-fickian diffusion	[41]
28	Stavudine	Matrix tablets	Eudragit RL 100, Ethylcellulose	Direct compression	Drug release from the tablets was slow and spread over 12h.	[42]
29	Stavudine	Matrix tablets	HPMC, Ethyl cellulose, Sodium CMC, Xantham gum, Gur gum, Gum karaya.	Wet granulation	Controlled release upto 12 hrs and is dependent upon polymer concentration. Release followed zero kinetics	[43]
30	Stavudine	Matrix tablets	lactose, microcrystalline cellulose	Direct compression	Sustained release upto 12 h and released followed zero order kinetics	[44]
31	Stavudine	Matrix tablets	HPMC K 100M , Ethyl cellulose	Wet granulation	Prolonged gastric residence time and controlled release upto 12 h	[45]
32	Stavudine	Matrix tablets	Eudragit RL 100, Ethyl cellulose	Direct Compression	Sustained release of drug for more than 12h	[46]
33	Stavudine	Matrix tablets	HPMCK100M, Sodium CMC	Direct Compression	Sustained release of drug up to 24h.Release	[47]

					followed zero order kinetics	
34	Stavudine	Matrix tablets	HPMC K100M, Sodium CMC	Dry granulation	Retention of the drug in the GIT for long period of time and sustaining the effect of drug.	[48]
35	Stavudine	Matrix tablets	Guar gum , Sodium CMC	non-aqueous granulation and compression	Sustained release of the drug over 24h.Release followed zero order kinetics	[49]
36	Stavudine	Matrix tablets	HPMC K4M, Eudragit RS100, PVPK90	Direct compression	Sustained release of the drug up to 12 h.	[50]
37	Stavudine	Nanoparticles	Eudragit RS 100	Nano precipitation	Sustained release of the drug over a period of 24 h	[51]
38	Zidovudine	Matrix tablets	Kollidon SR, HPMC K15M, K100M	Direct compression	Prolonged release of the drug over 12h	[52]
39	Zidovudine	Matrix tablets	Sodium CMC, HPMC, Eudragit L155, Xanthan gum	Wet granulation	Sustained release of drug over 12h.Release was by non fickian diffusion	[53]
40	Zidovudine	Matrix tablets	Methocel K100M /HPMC K100M, Polyethylene oxide (PolyoxWSR 301), Surelease.	Direct compression	Extended the drug release up to 12h. Release followed zero order kinetics	[54]
41	Zidovudine	Matrix tablets	HPMC E15LV and HPMC E50LV, Ethyl cellulose.	Wet granulation	Extended drug release upto 12h and overcomes the disadvantages of conventional tablets	[55]
42	Zidovudine	Matrix tablets	HPMCK100M.	Direct compression	Sustained drug release up to 24h. Release followed zero order kinetics	[56]
43	Zidovudine	Matrix tablets	Eudragit RS100 and RL100, Ethyl cellulose.	Direct compression	Controlled release of drug for extended periods of time	[57]
			HPMC K4 M,		Drug release was	

44	Zidovudine	Sustained Release Tablets	HPMC K10M and PVP K 30 , Eudragit RL 100, Ethyl Cellulose, Sodium CMC	Wet granulation	effectively maintained for 12h.Release was by non- fickian diffusion	[58]
45	Zidovudine	Matrix tablets	HPMC K4 M , Carbopol 934	Direct Compression	Slow and prolonged drug release for nearly 12 h.	[59]
46	Zidovudine	Matrix tablets	PVP-K90.	Wet granulation	Tablets sustained drug release for 12 h. Release followed first order kinetics	[60]
47	Zidovudine	Matrix tablets	Guar gum and polyvinyl pyrrolidone	Wet granulation	Matrix tablets maintained sustained release of drug over 12h.Release was diffusion controlled	[61]
48	Zidovudine	Matrix tablets	HPMC, Ethyl cellulose	Wet granulation	Extended drug release up to 16–20 h. Release was by non fickian diffusion	[62]
49	Zidovudine	Matrix tablets	PVP K30	Direct Compression	Extended sustained release of drug over 10-12h.Release was diffusion controlled	[63]
50	Zidovudine	Gasto retentive effervescent floating tablets	HPMC K4 M , Carbopol 934, SodiumCMC, Sodium alginate, Xanthan gum	Direct Compression	Controlled release of drug upto 12 h and is dependent on polymer used. Release followed zero order kinetics	[64]

CONCLUSION

Controlled release formulation is needed for several antiretroviral drugs to enhance their therapeutic efficacy and patient compliance. Controlled release matrix tablets and floating tablets of antiretroviral drugs have been successfully formulated employing polymers such as HPMC K100M, Carbopol 934P, and Natural gums like guar gum, xanthan gum, locust bean gum etc. Investigations are further needed in this area to develop newer techniques, methods and polymers for controlled release of antiretroviral drugs.

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