WORLD JOURNAL OF PHARMACEUTICAL RESEARCH
SJIF Impact Factor 8.074
Volume 7, Issue 14, 517-532. Review Article ISSN 2277– 7105

INNOVATIVE DRUG DELIVERY SYSTEMS FOR ANTI-RETROVIRAL DRUGS: AN OVERVIEW

Abdulsalam Alhalmi*[1,2], Marwan Altowairi[1], Marwan Almoiliqy[3] and Puneet Utreja[1]

[1]Faculty of Pharmaceutical Sciences, PCTE Group of Institutes, Punjab Technical University, India.

[3]Department of Pharmacology, Dalian Medical University, China.

[2]School of Pharmaceutical Education & Research, Jamia Hamdard University, New Delhi, India.

Article Received on
28 May 2018,

Revised on 18 June 2018,
Accepted on 08 July 2018

DOI: 10.20959/wjpr201814-12927

***Corresponding Author**
Dr. Abdulsalam Alhalmi
Faculty of Pharmaceutical Sciences, PCTE Group of Institutes, Punjab Technical University, India.

ABSTRACT

Acquired immunodeficiency syndrome (AIDS), one of the most serious viral diseases. It is a disease of which the body's immune system breaks down and is unable to fight off infections caused by human immunodeficiency virus (HIV). The treatment of such chronic disease conditions for long period, conventional formulations are administered in multiple doses, therefore have several disadvantages such as missed administration, fluctuations in drug levels which cause precipitation of adverse effects, and poor patient compliance. The most desirable and preferable formulations for such therapy are the sustained release tablet, because they offer better patient compliance, reduce dose frequency, reduce side effects and high safety margin for high potency drugs. The present review highlights various novels and controlled drug delivery systems that have been investigated by different researchers for achieving sustained drug delivery of antiretroviral drugs and for overcoming the limitations related to the conventional dosage forms of antiretroviral drugs.

KEYWORDS: AIDS; Novel Drug Delivery Systems, Anti-viral Drugs, HIV.

1. INTRODUCTION

Acquired immune deficiency syndrome (AIDS) is a disease caused by a retrovirus called human immunodeficiency virus (HIV.[1] After first infection, a patient may suffer of an influenza-like symptom for brief period followed by a long period without symptoms.

HIV can significantly effects the immunity function of body making the person much more sensitive to common infections, like tuberculosis, as well as infections and tumors that usually do not affect normal people. AIDS is considered to be an epidemic, and according to estimates from the Joint United Nations Programmed on HIV/AIDS (UNAIDS). Annually the number of AIDS deaths can be expected to increase for many years to come, unless more effective and patient-compliant antiretroviral medications are available at affordable prices.[2]

Signs and symptoms of HIV infection described in three main stages: Acute infections, Symptoms of acute infection. Clinical latency and AIDS.[3] AIDS is the final symptoms of the infection. An AIDS stage is often accompanied by the development of opportunistic infections such as pneumocystis pneumonia, skin lesions caused by Kaposi's sarcoma and severe weight loss.

HIV transmission are the direct sexual contact of infected person or by contact with blood or body fluid of HIV infected person.[4]

Antiretroviral therapy can slow the sequence of the disease, but not cure the disease.[5]

2. Antiviral Therapy

Recent treatment of AIDS mainly consists of highly active antiretroviral therapy (HAART) which slows sequences of the disease. Current HAART approaches are consists of combinations of at least three drugs belonging to at least two category of anti-retroviral agents.[6][7]

Six classes of antiretroviral agents are currently available for use summarized in table 1: [8]

Table 1: Antiretroviral drugs, trade name, their commercially available dosage forms, recommended adult dosage and half-lives.[8][9][10]

Drug class	Drug	Trade name	Dosage form	Recommended adult dosage	Half-life (h)
NRTIs	Zidovudine	Retrovir	Capsule, tablet, syrup, injection	200 mg tid or 300 mg bid	1.1
	Lamivudine	Epivir	Tablet, solution	150 mg bid or 300 mg qd	3-6
	Tenofovir	Viread	Tablet	300 mg qd	17
	Emtricitabine	Emtriva	Capsule	200 mg qd	10
	Abacavir	Ziagen	Film coated tablet	300 mg bid or 600 mg qd	1-2
	Didanosine	Videx	Tablet, solution	400 mg qd or 200 mg bid	1.3-1.6
	Stavudine	Zerit	Capsule, powder	30–40 mg bid	1- 1.6
	Zalcitabine	Hivid	Tablet	0.75 mg tid	1-3
NNRTIs	Nevirapine	Viramune	Tablet	200 mg bid	25-30
	Delavirdine	Rescriptor	Tablet	400 mg tid	5.8
	Efavirenz	Sustiva	Capsule, film, coated tablet	600 mg qd	40-50
	Etravirine	Intelence	Tablet	200 mg bid	30-40
PIs	Atazanavir	Reyataz	Capsule	400 mg qd	7
	Darunavir	Prezista	Tablet	600 mg bid	15
	Fosamprenavir	Lexiva	Tablet	1400 mg bid	7.7
	Indinavir	Crixivan	Capsule	800 mg tid	1.2-2
	Nelfinavir	Viracept	Tablet, powder	750 mg tid or 1250 mg bid	3.5-5
	Ritonavir	Norvir	Capsule, solution	600 mg bid	3-5
	Saquinavir	Nvirase	Capsule	1000 mg bid	1.5-2
	Tipranavir	Aptivus	Capsule	500 mg bid	5.5-6
Fusion inhibitor	Enfuvirtide	Fuzeon	Powder, Injectables	90 mg bid	3.8
CCR-5 inhibitor	Maraviroc	Selzentry	Tablet	300 mg bid	14-18
Integrase inhibitor	Raltegravir	Isentress	Tablet	400 bid	9

3. Problems in The Conventional Route of Anti-Retroviral Drugs

The adverse side effects of antiretroviral drugs during long term therapy for treatment of AIDS are most drawbacks of antiretroviral drugs. The complexity of treatment regimens (due to pill numbers and dosing frequency), short half-life, low bioavailability, poor CNS penetration and retention, hepatic first pass metabolism, patient noncompliance and high cost of the therapy are most disadvantages of antiretroviral drugs.[12][13] Because of all the problems associated with conventional dosage forms, the patient compliance and therapeutic effectiveness are very poor. To avoid the problems associated with the conventional dosage forms, different novel delivery systems for antiretroviral drugs have been investigated in the previous decade by many researchers worldwide. These systems sustain the release of the

drug, reduce side effects, dose and frequency of administration, increases bioavailability and therapeutic efficiency of the drug and finally improve the patient compliance.[14] The present review presents different novel drug delivery systems of antiretroviral investigated by different research groups all over the world. Various approaches studied for novel drug delivery systems of antiretroviral are discussed in this review.

4. Novel Drug Delivery Systems for Sustained and Controlled Delivery of Anti-Hiv Drugs

4.1. Microspheres

Microspheres or microparticles are solid small spherical particles (diameter 1-1000 μm), in which the drug dispersed either in solution or microcrystalline form. Microspheres are consisting of natural biodegradable proteins or synthetic polymers.

In general, microspheres have the potential interest by its ability to provide targeted, sustained and controlled drug release delivery.[15] The mucoadhesive microspheres have additional benefits, such as better absorption, improved bioavailability of the drugs and specific targeting of the drug to the absorption site.[16] The adhesion of the microspheres with mucosal tissue to enable the microspheres to release the drug for localized and to the systemic site.[17] Floating microspheres are also used for prolonging the residence time of drug in the stomach. As microspheres are a good means to prolong or sustain the drug delivery system, less frequent dosing can be achieved, which helps in improving patient compliance.[18] Many studies in the literature described the preparation of microspheres for delivering drugs into the body to sustain the action of the drug as summarized in Table 2. In this part, we review microspheres, which were tested for different antiretroviral agents.

Asha et al., 2011[19] prepare and evaluate zidovudine loaded chitosan microspheres for controlled drug release by emulsification method using gluteraldehyde as a cross-linking agent. The entrapment efficiency of microspheres loaded drug was 72-94% and the drug release was extended up to 12h.

Narasimharao et al., 2011[20] prepared lamivudine microspheres sustained release by using solvent evaporation technique. The drug release from microspheres was extended up to 12 h with ethylcellulose.

Khan et al., 2014[21] formulated and evaluated mucoadhesive microspheres of tenofovir disoproxil fumarate. Ionotropic gelation method was used to produce the microspheres. The optimized formulation retained its drug content and sustains the release for 24 h.

Sullad et al., 2011[22] prepared and evaluated microspheres of abacavir sulfate (AS) by carboxymethyl guar gum (CMGG) and an anionic semisynthetic GG derivative. The release of the drug was prolonged up to 28 h in both CMGG and GG matrices.

Josephine et al., 2011[23] prepared stavudine floating microspheres by an emulsion solvent diffusion method using Eudragit RS 100 as a rate controlling polymer. The buoyancy of all the prepared floating microspheres was 12h. The encapsulation efficiencies of the optimized microspheres formulation were up to 88%. In vitro release study of stavudine showed that a controlled release of a drug for over 12 h for all the prepared formulations.

Velmurugan et al., 2015[24] formulated and evaluated nevirapine mucoadhesive microspheres by HPMC K4M, HPMC K100 and Carbopol 940 in combination with sodium alginate as release controller. Nevirapine microspheres was prepared by ionotropic gelation method. The entrapment efficiencies ranged from 63.50 to 96.42% and the release of the nevirapine was controlled for about 12 h (98.65%).

Reddy et al., 2015,[25] designed sustained release efavirenz microspheres by the solvent evaporation method using varying proportions of polymers Eudragit RSPO and ethylcellulose 100 cpc, ethylcellulose N22. The results of in vitro release studies indicated all formulations released up to 12 h and the drug release of the optimized microspheres containing Eudragit RS PO was 96.82% at the end of 12 h.

Velmurugan et al., 2013[26] prepared mucoadhesive microspheres of maraviroc by ionotropic gelation method for retaining the drug release. The entrapment efficiency of the prepared mucoadhesive microsphere formulations was 84.22% at the end of 8 h. *In vitro* drug release of maraviroc from a mucoadhesive microspheres was (96.48%) at the end of 10 h.

Table 2: Microspheres as drug delivery systems for antiretroviral drugs.

S.No.	Drug name	Delivery system	Finding	Reference
1	Zidovudine	Microspheres	Drug release was sustained over 24 h.	[19]
2	Lamivudine	Microspheres	Drug release was extended up to 12 h.	[20]
3	Tenofovir	Mucoadhesive Microspheres	Drug release was sustained over 24 h.	[21]
4	Abacavir	Microspheres	Drug release was extended up to 28 h.	[22]
5	Stavudine	Floating Microspheres	Drug release was controlled for over12 h.	[23]
6	Nevirapine	Mucoadhesive Microspheres	Controlled release of the drug for about 12 h (98.65%).	[24]
7	Efavirenz	Microspheres	Drug release sustained for 12 h.	[25]
8	Ritonavir	Mucoadhesive Microspheres	Controlled release of drug for 12 h.	[26]
9	Maraviroc	Mucoadhesive Microspheres	Drug release was sustained for more than 10 h (96.48%).	[27]

4.2. Nanoparticles

Nanoparticles are colloidal particles able to deliver the drug to the target sites in the body and able to sustained drug release for long period. Nanoparticles have also been formulated for improving the efficacy of drugs with physicochemical problems and for targeted delivery of antiretroviral drugs to HIV-infected cells and to achieve extended drug release kinetics.[28][29] The nanoparticle drug delivery systems have several advantages such as improved efficacy, dosage reduction, decreased drug resistance and decreased in systemic toxicity.[30] A review of nanoparticles formulations for antiretroviral drugs investigated by different investigators has been summarized in Table (3) and described in this section.

Vyjayanthimala et al., 2014[31] formulated and evaluated chitosan nanoparticles of zidovudine for antiviral therapy using emulsion droplet coalescence method. The optimized formulations showed good drug release from the polymer. The cumulative drug release after 12 h was 75.89%.

Rathi et al., 2009[32] prepared lamivudine loaded nanoparticles based on polymethacrylic acid by nanoprecipitation method. The in vitro drug release profile from all the formulations was found to provide sustained release over a period of 24 h.

Baig et al., 2011[33] prepared abacavir sulfate nanoparticles by using in situ nanoemulsion–polymer cross-linking approach. Different ratios of alginates and abacavir sulfate (ag: abs) in the ratios of (1:1,1:2 and 1:3) were used. The encapsulation efficiency of 98.71% was

observed in the ratio 1:3 (ag: abs). In vitro drug release study showed sustained drug release over a period of 16 h.

Wilson et al., 2015[34] prepared and evaluated abacavir sulphate loaded albumin nanoparticles by desolvation method. Drug loading ranged from 1.2 to 5.9%w/w. The mean particle size was 418.2 nm and the surface charge was - 40.8 mV. The in vitro drug release was 51.36% w/w for 24 h.

Karthikeyan et al., 2013[35] prepared stavudine nanoparticles based on chitosan. The entrapment efficiency was found to be 83%. In vitro release studies revealed that the rate of drug release from the prepared nanoparticles was 93% in 24 h.

Devarajan et al., 2015[36] prepared nevirapine loaded gold nanoparticles using a biodegradable in house polymer polyethylene sebacate. Core-shell nevirapine nanoparticles comprising gold in the core and nevirapine loaded polyethylene sebacate as shell were successfully prepared using double emulsion solvent evaporation method followed by surface modification with macrophage mannose receptor targeting ligand concanavalin A by simple incubation. Nanoparticles with and without CON exhibited sustained release till 24 h in phosphate buffer pH 7.4.

Veerabhadram et al., 2012[37] prepared sfavirenz solid lipid nanoparticles by solvent emulsification. The optimized solid lipid nanoparticles had a particle size of 85.55±0.8 nm, zeta potential of -24.44± (0.4) mV, entrapment efficacy of 92±9.7% and final drug release of 83.75±2.54% in 48 h.

Singh et al., 2014[38] prepared atazanavir nanoparticles based on Eudragit RL100 by nanoprecipitation method. In vitro drug release from Eudragit RL100 nanoparticles was in a sustained manner for about 24 h.

Venkatesh et al., 2015[39] formulated nelfinavir loaded poly (lactic-co-glycolic acid) PLGA nanoparticles by nanoprecipitation method using PLGA and poloxomer 407. The size of the prepared nanoparticles and the zeta potential were found to be 185 ± 0.83 nm and 28.7 ± 0.09 mV, respectively. The entrapment efficacy and drug content of the optimized formulation were found to be 72 ± 0.47% and 36 ± 0.19% respectively. Sustained drug release up to 24 h from nanoparticles.

Shah et al., 2006[40] developed saquinavir-loaded poly (ethylene oxide)-modified poly (epsilon-caprolactone) nanoparticles by a solvent displacement method. The prepared nanoparticles had a mean particle diameter of approximately 200 nm. Sustained drug release was obtained at the end of 24 h.

Table 3: Nanoparticle as drug delivery systems for antiretroviral drugs.

S.No.	Drug	Drug delivery	Finding	Reference
1	Zidovudine	Nanoparticles	Drug release was sustained for 12 h.	[31]
2	Lamivudine	Nanoparticles	Drug release was sustained for 24 h.	[32]
3	Abacavir	Nanoparticles	Drug release was sustained for 16 h.	[33]
4	Abacavir	Nanoparticles	Drug release was sustained for 24h.	[34]
5	Stavudine	Nanoparticles	Drug release was sustained for 24 h.	[35]
6	Nevirapine	Gold nanoparticles	Drug release was sustained for 24 h.	[36]
7	Efavirenz	Solid lipid nanoparticles	Drug release was sustained for 48 h.	[37]
8	Atazanavir	Nanoparticles	Drug release was sustained for 24 h.	[38]
9	Nelfinavir	Nanoparticles	Drug release was sustained for 24 h.	[39]
10	Saquinavir	Nanoparticles	Drug release was sustained for 24 h.	[40]

4.3. Controlled and sustained administration by oral route

The oral route of administration is the most common mode of drug delivery into the body, due to flexibility in dosage form design and patient compliance. The tablet form is the most preferred among all oral dosage formulations because of the convenience of application and the ease of preparation on the industrial scale. The majority of oral tablet formulations are immediate release formulations. But the immediate release tablet formulations are generally associated with some limitations such as frequent administration, toxic side effects, low water solubility, drug fluctuations and poor bioavailability. Therefore, to overcome these drawbacks of conventional oral dosage forms, controlled and sustained release tablet formulations have been developed in order to improve the overall therapeutic benefit of anti-HIV drugs and to achieve effective therapy for many drugs.[41] Different types of controlled release tablet have developed e.g. extended release tablets, sustained release tablets, bilayered tablets, floating tablets, Bioadhesive tablets, etc.[42] The sustained release tablets decrease the frequency of dosing, improve therapeutic efficacy and avoid side effects associated with conventional tablets. Floating tablets prolong the gastric residence time of drug, thereby prolonging its duration of action and improving its bioavailability. Bioadhesive drug delivery systems are fabricated for adhesion on the mucosa by interacting with mucin in order to facilitate drug absorption over a prolonged period of time. Oral controlled release formulations for antiretroviral drugs are available in the market e.g. Retrovir, Epivir, Viread

and Ziagen as mention in Table (1). Table (4) describes various types of oral controlled release tablets.

Rao et al., 2012[43] formulated and evaluated gastro retentive effervescent floating formulation containing zidovudine by direct compression method**.** The in vitro buoyancy time range from 180 to 870 min. The optimized formulations show drug release ranges from 86.17 - 96.65% at the end of 12 h.

Rao et al., 2013[44] developed a floating tablets of lamivudine. The buoyant time for all tablets found to remain for a period > 24h in 0.1 N HCl. Lamivudine release from the optimized formulations was able to sustained release for over 24h.

Lohumi et al., 2013[45] developed and evaluated gastroretentive formulation of stavudine. All the formulations showed total floating time more than 24 h. The optimum formulations showed sustained drug release (98.434 ± 0.542%) up to 24 h.

Kumar et al., 2010[46] developed enteric coated tablets of didanosine by using wet granulation method. The in vitro drug release for 12 h revealed that no drug release was observed in first 2 h and gradually drug release was increased up to 12 h.

Rabinarayan et al., 2013[47] developed a floating tablet of ritonavir by direct compression technique. The in vitro drug release indicated extended release of ritonavir and more than 62% of the drug was released at the end of the 12 h for all the batches.

Rao et al., 2015[48] prepared the gas powered tablets of nevirapine by direct compression technique using polymers like HPMC K4M, K15M and Carbopal. The optimum formulations showed buoyancy lag time 14sec and the tablet remained buoyant for 12 h. The drug release from the formulations F3, F6 was found to be 99.99, and 99.61 in 20 h.

Table 4: Different controlled and sustained release tablets for antiretroviral drug.

S.No.	Drug	Drug Delivery System	Finding	Reference
1	Zidovudine	Floating drug delivery.	Drug release was sustained for12 h.	[43]
2	Lamivudine	Floating drug delivery.	Drug release was sustained for 24 h.	[44]
3	Stavudine	Gastroretentive tablets.	Drug release was sustained for 24 h.	[45]
4	Didanosine	Enteric coated tablets.	Drug release was sustained for12 h.	[46]
5	Ritonavir	Floating drug delivery.	Drug release was sustained for12 h.	[47]
6	Nevirapine	Gas powered tablets.	Drug release was sustained for 20 h.	[48]

4.4. Niosomal delivery system

Niosomes are defined as non-ionic surfactant vesicles, which are obtained by admixture of nonionic surfactant of alkyl or dialkyl polyglycerol ether and cholesterol with hydration in aqueous media.[49] They are found to be more stable system than the liposomal drug delivery system because of higher chemical stability of surfactants than that of phospholipids, which are used in liposomes preparation. Niosomes composed of hydrophilic and lipophilic moieties together. As a result, they can loading drug with a wide range of solubility.[50] Recently niosomes have been found to be useful in targeted delivery of antiretroviral drug.[51] A different niosomal delivery system for antiretroviral drug have been investigated by are summarized in Table 5.

Shreedevi et al., 2016[52] formulated stavudine-based niosomes using ether injection method. The optimum formulation was sustained the drug release for 24 h.

Begum et al., 2014[53] co-encapsulated stavudine and lamivudine in niosomal MLVs. The maximum entrapment efficiency of drug (92.64%) was achieved with the formulation containing the drug –lipid ratio of 150:40% w/w. In vitro release data showed that release profile followed zero order kinetics and drug release mechanism was of diffusion. Stavudine and Lamivudine niosomes controlled drug release even after 24h.

Meenakshi et al., 2016[54] prepared lamivudine maltodextrin based proniosomes by the slurry method using different non-ionic surfactants (Span 40, Span 60, Tween 60) in various concentrations keeping the concentration of cholesterol, maltodextrin as constant. Further proniosomes converted into niosomes by simple hydration method. The highest entrapment efficiency was found for optimized formulation (95.02%) and the cumulative percentage drug release in 24 h was (93.53%).

Ruckmani et al., 2010[55] prepared and evaluated niosomes. The entrapment efficiency of drug was high when zidovudine niosomes formulated with tween 80 and enhanced drug release for a longer time (88.72%) over 12 h.

Bhargavi et al., 2016[56] formulated emtricitabine as a niosomal by thin layer evaporation (TLE)-paddle stirring method. The entrapment efficiency and the mean particle size were found to be 64.45±1.14% and 154±4 nm, respectively. Central nervous system penetration

was enhanced by loading emtricitabine as niosomes, therfore niosomes can be considered as a potential alternative to improve brain targeting.

Table 5: Different niosomal delivery system for antiretroviral drug.

S.No.	Drug	Drug delivery system	Finding	Reference
1	Stavudine	Niosome	Drug release was sustained for 24 h.	[52]
2	Lamivudine	Niosome	Drug release was controlled and sustained even after 24 h.	[53]
3	Lamivudine	Proniosome	Cumulative percentage drug release in 24 h was (93.53%).	[54]
4	Zidovudine	Niosome	Drug release was sustained over 12 h.	[55]
5	Emtricitabine	Niosome	Improved CNS penetration of the drug	[56]

5. CONCLUSION

Conventional drug delivery involved in antiretroviral, such as compressed tablet for oral administration or a solution for IV administration, such dosage form have several limitations such as requirement of high dosage, dose frequency, low affectivity, high adverse effects. In the last decades different novel and controlled drug delivery systems are being investigated to overcome the limitations of the conventional drug delivery, to decrease drug degradation, to minimize the side-effects and to improve drug bioavailability. Several drug delivery and drug targeting systems are currently under development as a means to enhance the effective delivery of antiretroviral drugs for HIV prevention and therapy. As a conclusion of this review paper introduce the most recent approaches of novel drug delivery system for anti-HIV drugs, (microspheres, nanoparticles, perioral controlled delivery systems and niosomes) that have been found to be potentially beneficial in terms of many aspects since they: a) reduce the dosing frequency, b) increase the bioavailability of anti-HIV drugs, c) improve physicochemical properties of drugs such as low solubility as well as stability and d) reduce the side effects.

Conflicts of Interest

The authors declare they have not conflict of interest.

ACKNOWLEDGEMENT

Special thanks to my supervisor, Dr. Puneet Utreja for his excellent guidance and support throughout my entire course. Great thanks to the Faculty of Pharmaceutical Science, PCTE group of institutes, for providing the required facilities for the completion of this article.

REFERENCES

1. Sosnik A, Chiappetta DA, Carcaboso ÁM. Drug delivery systems in HIV pharmacotherapy: What has been done and the challenges standing ahead. Vol. 138, Journal of Controlled Release. 2009; 2–15.
2. Kulkarni S V., Ranjit KP, Shankar MS, Someshwara RB, Ashok Kumar P, Ramesh B. Formulation and in vitro evaluation of sustained release matrix tablet of stavudine. Asian J Pharm Clin Res., 2010; 3(3): 215–7.
3. Hoenigl M, Green N, Camacho M, Gianella S, Mehta SR, Smith DM, et al. Signs or symptoms of acute HIV infection in a cohort undergoing community-based screening. Emerg Infect Dis., 2016; 22(3): 532–4.
4. Fatahzadeh M, Schwartz RA. Human herpes simplex virus infections: Epidemiology, pathogenesis, symptomatology, diagnosis, and management. Vol. 57, Journal of the American Academy of Dermatology, 2007; 737–63.
5. Palella FJ, Delaney KM, Moorman AC, Loveless MO, Fuhrer J, Satten GA, et al. Declining morbidity and mortality among patients with advanced human immunodeficiency virus infection. HIV Outpatient Study Investigators. N Engl J Med., 1998; 338(13): 853–60.
6. World Health Organization. Antiretroviral Therapy for HIV Infection in Adults and Adolescents: Recommendations for A Public Health Approach. World Heal Organ., 2006; 1–134.
7. Kinch MS, Patridge E. An analysis of FDA-approved drugs for infectious disease: HIV/AIDS drugs. Drug Discov Today., 2014; 19(10): 1510–3.
8. Singh N, Singh R. An Introduction to the Approaches of Novel Drug Delivery Systems for Acquired Immune Deficiency Syndrome (AIDS) Maturation inhibitors, 2016; 2(1): 1–14.
9. Vedha Hari BN, Devendharan K, Narayanan N. Approaches of novel drug delivery systems for Anti-HIV agents. Vol. 5, International Journal of Drug Development and Research, 2013; 16–24.
10. Katzung BG, Masters SB, Trevor AJ. Basic & clinical pharmacology. A Lange medical book., 2012; xiii: 1229 .
11. Rathbun RC, Lockhart SM, Stephens JR. Current HIV treatment guidelines--an overview. Curr Pharm Des., 2006; 12(9): 1045–63.
12. Devi K, Pai R. Antiretrovirals: Need for an effective drug delivery. Indian J Pharm Sci., 2006; 68(1): 1–6.

13. Mallipeddi R, Rohan LC. Progress in antiretroviral drug delivery using nanotechnology. Vol. 5, International Journal of Nanomedicine, 2010; 533–47.
14. Richman DD. Introduction: challenges to finding a cure for HIV infection. Curr Opin HIV AIDS., 2011; 6(1): 1–3.
15. Kim KK, Pack DW. Microspheres for Drug Delivery. Biol Biomed Nanotechnol, 2006; 19–50.
16. Alagusundaram M, Madhu Sudana Chetty C, Umashankari K, Badarinath AV, Lavanya C, Ramkanth S. Microspheres as a novel drug delivery sysytem - A review. Int J Chem Tech Res., 2009; 1(3): 526–34.
17. Vasir JK, Tambwekar K, Garg S. Bioadhesive microspheres as a controlled drug delivery system. Vol. 255, International Journal of Pharmaceutics, 2003; 13–32.
18. Genta I, Conti B, Perugini P, Pavanetto F, Spadaro a, Puglisi G. Bioadhesive microspheres for ophthalmic administration of acyclovir. J Pharm Pharmacol, 1997; 49(8): 737–42.
19. Asha K, Vikash D. Formulation and evaluation of zidovudine loaded chitosan microspheres for controlled release. Int J Drug Dev Res., 2012; 4(1): 96–105.
20. Lettre DP, M SCP, Raj SB, Ajay M, Babu BN, Audinarayana N, et al. Formulation and evaluation of lamivudine enclosed alginate microbeads, 2011; 3(6): 294–304.
21. Khan AB, Thakur RS. Formulation and evaluation of mucoadhesive microspheres of tenofovir disoproxil fumarate for intravaginal use. Curr Drug Deliv., 2014; 11(1): 112–22.
22. Guo C, Zhou L, Lv J. Effects of expandable graphite and modified ammonium polyphosphate on the flame-retardant and mechanical properties of wood flour-polypropylene composites. Polym Polym Compos., 2013; 21(7): 449–56.
23. Josephine LJJ, Mehul RT, Wilson B, Shanaz B, Bincy R. Formulation and in vitro evaluation of floating microspheres of anti-retro viral drug as a gastro retentive dosage form. Int J Res Pharm Chem., 2011; 1(3): 519–27.
24. Ararath D, Velmurugan S. Formulation and Evaluation of Nevirapine Mucoadhesive Microspheres. Int J Pharm Pharm Sci., 2015; 7(6): 342–8.
25. Venkateswara Reddy B, Krishnaveni K. Formulation and evaluation of efavirenz microspheres. Der Pharm Lett., 2015; 7(6): 1–9.
26. Velmurugan S, Ali MA. Formulation and evaluation of Maraviroc mucoadhesive microsheres by Ionotropic gelation method. Int J Pharm Pharm Sci., 2013; 5(SUPPL.4): 294–302.

27. Velmurugan S, Ali MA. Development and evaluation of ritonavir mucoadhesive microspheres. Asian J Pharm Clin Res., 2014; 7(5): 47–52.
28. Mohanraj V, Chen Y, Chen M &. Nanoparticles – A Review. Trop J Pharm Res Trop J Pharm Res., 2006; 5(June): 561–73.
29. Bender AR, Von Briesen H, Kreuter J, Duncan IB, Rubsamen-Waigmann H. Efficiency of nanoparticles as a carrier system for antiviral agents in human immunodeficiency virus-infected human monocytes/macrophages in vitro. Antimicrob Agents Chemother, 1996; 40(6): 1467–71.
30. Dhana lekshmi UM, Poovi G, Kishore N, Reddy PN. In vitro characterization and in vivo toxicity study of repaglinide loaded poly (methyl methacrylate) nanoparticles. Int J Pharm., 2010; 396(1–2): 194–203.
31. Vyjayanthimala T. Formulation and evaluation of zidovudine loaded. Int J Biopharm, 2014; 5(1): 1–4.
32. Tamizhrasi S, Shukla A, Shivkumar T, Rathi V, Rathi JC. Formulation and evaluation of lamivudine loaded polymethacrylic acid nanoparticles. Int J Pharm Tech Res., 2009; 1(3): 411–5.
33. Vetrichelvan T, Baig IS. Preparation and Invitro Characterization of Slow Release Abacavir Sulfate Nanoparticles in Alginates., 2011; 2(2): 60–8.
34. Wilson B, Paladugu L, Priyadarshini SRB, Jenita JJL. Development of albumin-based nanoparticles for the delivery of abacavir. Int J Biol Macromol., 2015; 81: 763–7.
35. Karthikeyan D, Srinivas M, Kumar CS. Formulation and Evaluation of Stavudine Nanoparticles. Int J Nov Trends Pharm Sci., 2013; 3: 24–32.
36. Kapoor S. Preparation, Characterization, and Surface Modification of., 1998; 3(17): 1021–5.
37. Madhusudhan A, Reddy GB, Venkatesham M, Veerabhadram G. ISSN : 2249-0337 Original Article Design and Evaluation of Efavirenz loaded Solid Lipid Nanoparticles to Improve the Oral Bioavailability, 2012; 2(4): 84–9.
38. Singh G, Pai RS. Atazanavir-loaded Eudragit RL 100 nanoparticles to improve oral bioavailability: optimization and *in vitro* / *in vivo* appraisal. Drug Deliv., 2016; 23(2): 532–9.
39. Kar RK, Mohapatra S, Barik BB. Design and characterization of controlled release matrix tablets of zidovudine. Asian J Pharm Clin Res., 2009; 2(2): 54–61.
40. Shah LK, Amiji MM. Intracellular delivery of saquinavir in biodegradable polymeric nanoparticles for HIV/AIDS. Pharm Res., 2006; 23(11): 2638–45.

41. Ojewole E, Mackraj I, Naidoo P, Govender T. Exploring the use of novel drug delivery systems for antiretroviral drugs. Vol. 70, European Journal of Pharmaceutics and Biopharmaceutics, 2008; 697–710.
42. Jaimini M. Sustained Release Matrix Type Drug Delivery System: a Review. J Drug Deliv Ther [Internet]., 2012; 2(6): 142–8. Available from: http://jddtonline.info/index.php/jddt/article/view/340
43. Jiang H, Tian R, Hu W, Jia Y, Yuan P, Wang J, et al. Formulation and evaluation of gastroretentive floating drug delivery system of dipyridamole. Drug Dev Ind Pharm., 2015; 41(4): 674–80.
44. Vidyadhara S, Nagendran I, Sasidhar RLC, Devi VA, Swapna K. Formulation and evaluation of controlled release floating matrix tablets of Stavudine. Asian J Pharm., 2012; 6(4): 259–65.
45. Vv P, Sarkar S, Tribedi S, Mathappan R, Mathew ST. Research and Reviews : Journal of Pharmacy and Pharmaceutical Sciences Formulation and Evaluation of Orodispersible Tablets of Salbutamol Sulphate, 2013; 2(3): 26–36.
46. Kumar KLS, Ashokkumar S, Ezhilmuthu RP. Formulation and Evaluation of Didanosine Enteric Coated Sustained Release Tablet., 2010; 2(3): 126–31.
47. Moumita BISWAS, Roop Narayan GUPTA, Rabinarayan PARHI, Kalyan Kumar SETHI SKS. Formulation and in vitro evaluation of gastroretentive floating drug delivery system of ritonavir., 2013; 10(1): 69–86.
48. Rao NGR, Kumar GV, Priyanka V. Design and development of Nevirapine gas powered system for controlled release N. Asian J Biochem Pharm Res., 2015; 5(3): 146–57.
49. Mujoriya RZ, Dhamande K, Bodla RB. Niosomal drug delivery system - a review. Int J Appl Pharm., 2011; 3(3): 7–10.
50. Nerkar AG, Lade KS, Gadhave N a, Sawant SD. Available online through Chiral switches : A Review. J Pharm Res., 2011; 4(40): 1300–3.
51. Ag Seleci D, Seleci M, Walter JG, Stahl F, Scheper T. Niosomes as nanoparticular drug carriers: Fundamentals and recent applications. J Nanomater, 2016; 2016(Figure1).
52. Shreedevi HM, Nesalin JAJ, Mani TT. Development and evaluation of stavudine niosome by ether injection method., 2016; 7(1): 38–46.
53. Sinica DP, Begum MY, Dasari S, Sudhakar M, Lakshmi BVS, Manga K, et al. Pelagia Research Library Development and evaluation of co-encapsulated stavudine and lamivudine niosomes for the controlled delivery., 2014; 5(1): 1–10.
54. Elangoo MM an. K. Preparation and evaluation of lamivudine proniosomes for HIV

infection., 2014; 3(7): 50–78.

55. Ruckmani K, Sankar V. Formulation and optimization of Zidovudine niosomes. AAPS Pharm Sci Tech., 2010; 11(3): 1119–27.
56. Sheela S, Bhargavi N, Mohanavelu N, Perumal PS. Formulation and Evaluation of In Vitro Blood-Brain Barrier Penetration of Emtricitabine Niosomes Using Immobilized Artificial Membrane Phosphatidyl Choline Column Chromatography, 2016; 6(September).