ISSN PRINT 2319 1775 Online 2320 7876

Research paper UGC CARE Listed (Group -I) Journal Volume 11, Iss 11, Nov 2022

DESIGN, DEVELOPMENT OF ADVANCES NANOFORMULATION ON DELIVERY FOR BRAIN FUNCTIONS AND BIOAVAILABILITY ACTIVITY FOR ANTI-VIRAL DRUG

Naik Ashok Ramrao [1], Dr. Vijaysinh Uttamrao Sable[1] and Dr. Rakesh Meel[1]

[1] Department of Pharmacy, Sunrise University, alwar, Rajasthan

[*]Email – Pintunaike6484@gmail.com

ABSTRACT- HIV, which causes AIDS, is one of the deadliest diseases and the sixth leading cause of death. The reported poor bioavailability of non-nucleoside reverse transcriptase inhibitors used to treat HIV infection is related to first pass metabolism, protein binding and enzyme metabolism. They are also less permeable to the blood-brain barrier. He biomimetic architecture, the ability to hijack host immune responses, continuous antigen shifting, and drafting are the major critical factors that are responsible for the unavailability of a concrete therapeutic regimen against viral infections. Further, inappropriate pharmacodynamic physicochemical and biological parameters such as low aqueous solubility, poor permeability, high affinity for plasm proteins, short biological half-lives, and fast elimination from the systemic circulation are the major critical factors that govern the suboptimal drug concentration at the target site that leads to the development of drug resistance. However, size, shape, charge, and surface topology of nanoparticles are the greater influential factors that determine target-specific drug delivery, optimum cellular uptake, degree of opsonization by the host immune cells, drug retention time, transcytosis, the extension of biological half-life, in vivo stability, and cytotoxicity. The review will enlighten the elaborative role of nanotechnology-based drug delivery and the major challenging aspect of clinical safety and efficacy. Various parameters of Efavirenz SLN gel were evaluated, such as gel temperature, pH, viscosity, light transmittance, muco-adhesive strength, diffusion, and in vitro and ex vivo dissolution studies. Drug release was found to be optimal for zero-order release kinetics (R2 = 0.3), suggesting that drug release is concentration-sensitive and diffusion-controlled. In vivo pharmacokinetic studies have shown that it is possible to successfully eradicate HIV in the brain and cure HIV patients after intranasal administration, and many of these

ISSN PRINT 2319 1775 Online 2320 7876

Research paper UGC CARE Listed (Group -I) Journal Volume 11, Iss 11, Nov 2022

problems are voluntarily overcome by the use of advanced anti-inflammatory drugs developed with nano-technology. These delivery systems carry antibodies in nanoparticles that can be made from synthetic or natural materials. However, due to health and environmental concerns, there is interest in developing antibiotics from natural products such as lipids.

Keyword: Nanoformulation, Anti-Viral Drugs, transcytosis, organic and inorganic nanocarrier system, pharmacokinetics, targeted delivery

Introduction-

Current treatments using antiretroviral drugs for HIV infection are effective at lowering plasma levels, but not effective at eliminating the virus in other areas, such as the central nervous system, because they are inaccessible and cannot be stored in cellular and anatomical reservoirs where the virus can center. . . The central nervous system is the most important HIV repository [9]. With limited access to anti-AIDS drugs, the brain is thought to be a haven for the virus. This not only causes immunity, but mental function improvement, movement symptoms or mild neurocognitive impairment (MDR), HIV-associated dementia (HAD), HIV encephalitis (HIVE), and in many cases even death. he development of an effective treatment against viral infections remains a greater challenging arena in front of the global scientific community. The various critical factors like continuous viral antigen shifting and drafting (alteration of surface proteins (antigen) due to mutation), non-specific drug targeting, suboptimal drug concentration at the target site, and development of drug resistance are the crucial factors that are responsible for ineffective therapeutic regimen against viral infections [2]. The major antiviral drug regimen consists of remdesivir, oseltamivir, zidovudine, zalcitabine, stavudine, abacavir, nelfinavir, ritonavir, efavirenz, etc., Other class of antiviral therapeutics such as acyclovir, ritonavir, and efavirenz shows poor aqueous solubility 2.25, 1.2, and 8.85 µg/L respectively at pH 6.8 which restrict their systemic absorption from the intestinal site that leads to poor drug bioavailability [34]. Addressing such issues, nanotechnology-based drug delivery is emerging as an alternative approach for improving the therapeutic efficiency by altering the physicochemical properties of the antiviral drugs. Tracking the effectiveness and safety profile, there are still many critical aspects like immunogenicity, target specificity, and compatibility in the biological environment that are closely associated with the nanotechnology-integrated nanomedicines. In contrast,

ISSN PRINT 2319 1775 Online 2320 7876

Research paper UGC CARE Listed (Group -I) Journal Volume 11, Iss 11, Nov 2022

viruses have been armed with a different strategy to evade humoral and cellular immune responses for about millions of years of evolution [36]. Viral physiochemical features that include size, shape, hydrophobicity, and surface charge define many of these stealth activities.

A virus is the microscopic particulate of dimensions ranging from 1 to 100 nm that fuses directly at the plasma membrane followed by various endocytic processes such as clathrin-mediated endocytosis, caveolin-mediated endocytosis, macropinocytosis, and phagocytosis that reach intracellular compartments. After successful internalization of viral components (both enveloped and non-enveloped), it alters the cellular environmental factors, like pH, connection with a target cell, or the activity of proteolytic enzymes, that causes a conformational change in specific proteins that manipulate the host immune responses [37].

Aim of the research work- The aim of this study is to design and manufacture nanoparticles of the antiviral drug efavirenz, to increase their bioavailability in the HIV reservoir area by delivering them to the brain, to conduct research and to compare formulations of existing formulations.

Blood –Brain Barrier- BBB (Blood-Brain Barrier) The BBB is an important barrier that prevents macromolecules, hydrophilic molecules, microorganisms, or nanoparticles from entering the brain [34]. The blood-cerebrospinal fluid barrier (BCSFB), composed of choroid plexus epithelial cells, also plays a role in nutrient and xenobiotic permeability. Access to the brain is limited and well-controlled, mainly due to three types of damage.

1. Physical Barrier- The BBB shows the largest surface area (approximately 20 m2), has weak endothelial cells with tight junctions preventing transport, lacks endothelial fenestrations, and reduces the rate of pinocytosis on the luminal side. The BCSFB problem occurs because there is a layer of polarized epithelial cells around the windowed capillaries held together by tight junction proteins.
2. Biological Barrier- Expression and function of various receptors, ion channels, and efflux/efflux transporters that regulate transport. In particular, ATP-binding cassette (ABC) membrane-associated transporters such as P-glycoprotein (P-gp), multidrug resistance-associated protein (MRP), and breast cancer protein (BCRP, ABCG2) play an important role in restrictions. . Many Penetration drugs, including anti-cancer drugs and anti-HIV drugs.
3. Metabolic Barrier- Metabolic enzymes can inhibit transport. These transporters and enzymes may also cause drug-drug interactions that can lead to treatment failure and/or toxicity.

ISSN PRINT 2319 1775 Online 2320 7876

Research paper UGC CARE Listed (Group -I) Journal Volume 11, Iss 11, Nov 2022

Design of experiment- Its products are designed to meet the patient's needs and product needs. Drug development should include the definition of quality product (QTPP), identification and determination of critical features (CQAs), selection of appropriate manufacturing processes, determination of control strategies, identification of possible equipment and procedures affecting the CQA product. A method can facilitate continuous improvement and innovation in production and throughout the life of the product [16-18].In the current study, drug identification, selection of different products, social studies etc. Many preliminary studies such as particle size and maximum encapsulation of drug Efficacy in SLN [19, 20].

Preformulation studies - The main components of solid lipid nanoparticle systems include drugs, lipids and surfactants. After identifying the drug, various materials were selected as components of the proposed system. This selection was based on drug solubility and ability to form small particles. The selection was also based on the component's safety profile and approval status.

Drug-Excipients Compatibility Study- infrared spectra of pure chemicals stored at 25 ± 2 OC, 60% ± 5% relative humidity for 7 days, as well as physical mixtures of chemicals and selected materials, were recorded using an FT-IR spectrophotometer (Bruker Alpha-one, Bruker Optik). , Germany) in the range of 4000–400 cm-1 and compared significant changes

Figure 02 : Formulation of solid lipid nanoparticles by high pressurehomogenization

Nanotechnology-Based Drug Delivery System for the Treatment of Viral Infections

As per the Center for Disease Control and Prevention (CDC) guidelines, the appearance of widespread resistance against the strains of influenza A viruses adamantanes (amantadine and rimantadine) a class of antiviral drugs used are not recommended by the physicians in the USA. In addition, antiviral drugs like ganciclovir and valganciclovir (cytomegalovirus), acyclovir

ISSN PRINT 2319 1775 Online 2320 7876

Research paper UGC CARE Listed (Group -I) Journal Volume 11, Iss 11, Nov 2022

(herpes simplex virus), lamivudine, adefovir, telbivudine, entecavir, and tenofovir (hepatitis B virus) show clinical evidence for drug resistance [42]. **Muco-adhesive strength-** Mucoadhesion was determined by a modified two-disc balance [37]. According to the literature review, although there are many in vitro and in vivo studies of the efficacy of mucoadhesive drug delivery systems, surprisingly, there is still no established protocol to measure mucoadhesion or can be done according to its quality. Mucoadhesion Strength Method. In vitro testing with a two-disc balance is the best and easiest way to evaluate the mucoadhesive properties of formulations [43, 44]. In this way, as shown in Figure 3.3, one side of the scale is covered with wooden blocks and the other side with a container of water.More than 20 µl of test sample gel in contact with cellophane film (1 cm2) adhered to the horizontal end of the water box and on the perfect surface. Water was slowly added dropwise until the cellophane membrane separated from the gel.

Weight in grams of water required to separate the two surfaces was measured

$$F = w \times g$$

Where F is the muco-adhesion force (dynes / cm^2),
w is the minimum weight required to break the bond (grams), g is the acceleration due to gravity (cm/s^2).

Drug Release Profile

***In-vitro* drug diffusion profile-** In vitro drug diffusion curves of SLN dispersions and EFV-loaded SLN gels were obtained using the dialysis bag/dialysis bladder method [7,24,48] as well as Franz diffusion cells [18,36,48]. For the Dialysis bag, the SLN dispersion and bulk suspension are packaged in a filter bag 110 (LA 395), Himedia, cut at 12000 Da) and extracted in 50 ml of methanolic phosphate buffered saline (pH 6.4) in a glass beaker, 40% v/v) [6, 7]. The beaker was placed on a magnetic stirrer and mixed with magnetic beads and covered with parafilm to prevent evaporation loss during the experiment [46]. Fractions are removed from the receptor chamber at 24-hour intervals and replaced with an equal volume of fresh diffusion medium.

***Ex-vivo* drug release profile-** In vitro release studies were performed in the nasal cavities of slaughtered goats using Franz diffusion cells [18, 39]. Carefully remove the proboscis and remove the tissue. Mount the severed nose in a Franz diffusion cell and fill the receptor chamber with methanolic phosphate buffer (pH 6.4, 40% v/v). Place the cells on a magnetic stirrer for gentle shaking and keep the temperature at 34 ± 0 °C. Place 5 EFV preparations (0.5 mL) on the

ISSN PRINT 2319 1775 Online 2320 7876

Research paper UGC CARE Listed (Group -I) Journal Volume 11, Iss 11, Nov 2022

donor site. Fractions are removed from the receiving chamber at 24-hour intervals and replaced with an equal volume of fresh diffusion medium. Aliquots were analyzed spectrophotometrically at 247 nm.

In-vivo studies- In vivo studies were performed in adult albino Wistar mice. Animal study protocols were approved by the Animal Ethics Committee (IAEC) and Animal Control and Care Committee (CPCSEA) [PIPH 04/15 CPCSEA921/PO/Ere/S/05/CPCSEA]. Animals were housed in polypropylene cages for mice. Rice bran was used as bedding. Laboratory rats were provided ad libitum with granulated food and purified drinking water. Rats were divided into two groups. Group I (a test group) consisted of 6 animals and the established SLN formulation (equivalent to 0.06 mg efavirenze) was administered intranasally. The second group (standard) consists of 6 animals speaking commercial - EFAVIR - efavirenz capsules.(Powder equivalent to 25 mg efavirenz capsules, dispersed in 1 ml of water). This dose is calculated as the Human Equivalent Dose (HED) according to FDA guidelines. Plasma samples were collected from all animals and animals were sacrificed within 24 hours with an overdose of sodium pentobarbital. Brains were isolated, weighed, homogenized in PBS pH 6.4 at 5000 rpm using the Silent Crusher M homogenizer (Heidolph, Germany), centrifuged, and the supernatant collected for drug concentration determination [55].The amount of drug in plasma and brain homogenates is determined using HPLC, a developed and validated method for estimating efavirenz in plasma. Tenofovir disoproxil fumarate was used as an internal standard. Brain:plasma ratio, bioavailability and relative bioavailability were calculated using the formula brain:plasma = concentrate. Brain drug concentration/concentration Amount of drug in plasma fraction Bioavailability = Bioavailable dose/Used dose Relative bioavailability = Systemic drug availability/Systemic availability of an oral standard of the same drugs.

Results

Identification of Drug- Before starting its construction, it is necessary to determine and ensure the purity of the purchased drug. Analytical tests and decisions to determine the appearance, solubility and melting point of chemical samples are summarized in Table 3.

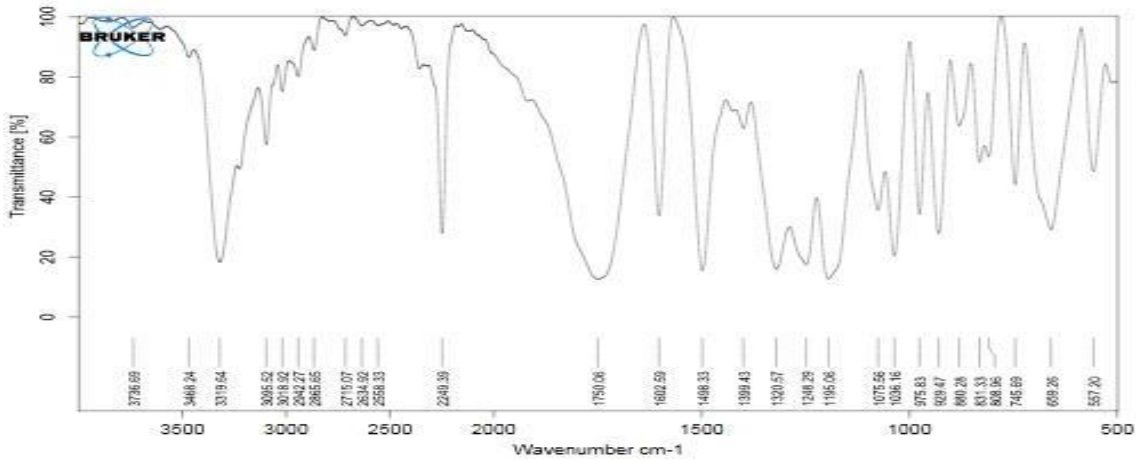
TABLE 3: Identification tests for EFV with the inferences

Parameters	Observations	Reported [1]	Inferences
Appearance	White powder	White to almost white powder	Complies

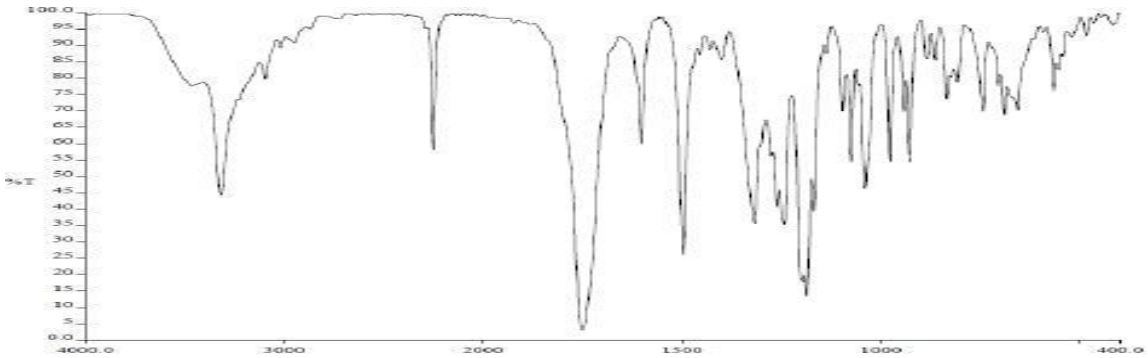
ISSN PRINT 2319 1775 Online 2320 7876

Research paper UGC CARE Listed (Group -I) Journal Volume 11, Iss 11, Nov 2022

Solubility	Practically insoluble in water (10 mg insoluble in >100 ml) Freely soluble in methanol (10 mg in < 1 ml)	Practically insoluble in water Freely soluble in methanol	Complies Complies
Melting point	139-142^{0}C	138 – 142 ^{0}C	Complies



(a)



(b)

Figure 2: IR spectra (a) Observed spectra of EFV (b) Reported spectra of EFV

TABLE 4: Major peaks observed and reported for EFV in IR spectra:

ISSN PRINT 2319 1775 Online 2320 7876

Research paper UGC CARE Listed (Group -I) Journal Volume 11, Iss 11, Nov 2022

Observed (cm^{-1})	**Reported (cm^{-1})**	**Inferences [3]**
3319.64	3500-3100	N-H stretching
2249.39	2250-2100	C= C (Alkyne)
1750.06	1750-1730	C=O of ester
1602.59	1680-1630	C=O of amide
1498.33	1350-1000	C-N
1036.16	1300-1000	C-O

Conclusion- Advanced developments in nanomedicine design and engineering have provided many privileges over the traditional approach of drug administration for the prevention and treatment of viral infections. The dominance of nanomedicine approaches lies in the presentation of unique attributes such as nanoscale dimensions, high surface-to-volume ratio, the versatility of surface functionalization to achieve the desired selectivity, and biocompatibility. The present investigations, it may be concluded that solid lipid nanoparticles of a poorly soluble drug efavirenz were successfully developed and optimized using the systematic approach of design of experiments (DoE) by high pressure homogenization technique. Thermo sensitive *in-situ* gel was prepared with the optimized SLN dispersion. it may be concluded that the developed formulation has better potential to target brain where the HIV viruses are reported to harbor even with low dose of efavirenz, rendering the treatment more cost-effective as well and acceptable to patients because of convenience of application of *in-situ* gelling formulation. Hence, the developed formulation, after necessary investigations of clinical trials, has the promising potential for an attempt to completely eradicate HIV reservoir and cure AIDS.

References

1. Kawabata Y, Wada K, Nakatani M, Yamada S, Onoue S., (2011). Formulation design for poorly water-soluble drugs based on biopharmaceutics classification system: Basic approaches and practical applications. *Int J Pharm*; 420(1):1-10.

ISSN PRINT 2319 1775 Online 2320 7876

Research paper UGC CARE Listed (Group -I) Journal Volume 11, Iss 11, Nov 2022

2. Kawakami K., (2012). Modification of physicochemical characteristics of active pharmaceutical ingredients and application of supersaturatable dosage forms for improving bioavailability of poorly absorbed drugs. *Adv Drug Deliv Rev*.;64(6):480-495.

3. Wong HL, Wu XY, Bendayan R., (2012). Nanotechnological advances for the delivery of CNS therapeutics. *Adv Drug Deliv Rev*. ;64(7):686-700.

4. Cundy KC, Lynch G, Lee WA., (1997). Bioavailability and metabolism of cidofovir following topical administration to rabbits**.** Antiviral Research ;35(2):113-122.

5. List of Viral Diseases. [Online]. Available: http://doctors-hospitals-medical-cape-town-south-africa.blaauwberg.net/details.php?id=768. [Accessed 25 June 2016]

6. Infectitious viral diseases. [Online]. Available: usa.gov/search?affiliate=ri.gov&query=viral&sitelimit=health.ri.gov [Accessed 12 November 2015]

7. Global HIV/AIDS Overview. [Online]. Available: https://www.aids.gov/federal-resources/around-the-world/global-aids-overview/. [Accessed 12 November, 2015]

8. WHO | HIV/AIDS. [Online]. Available: http://www.who.int/gho/hiv/en/. [Accessed 12 November, 2015.

9. Rao KS, Ghorpade A, Labhasetwar V., (2009). Targeting anti-HIV drugs to the CNS. *Expert Opin Drug Deliv*.;6(8):771-784.

10. Hasegawa T, Kawaguchi T., (2002). Delivery of Anti-Viral Nucleoside Analogues to the Central Nervous System. *Curr Med Chem -Anti-Infective Agents*;1(1):55-63.

11. Corbau R, Mori J, Phillips C, et al., (2010). Lersivirine, a nonnucleoside reverse transcriptase inhibitor with activity against drug-resistant human immunodeficiency virus type 1. *Antimicrob Agents Chemother*;54(10):4451-4463.

12. DrugBank: Efavirenz. [Online]. Available: http://www.drugbank.ca/drugs/DB00625.

ISSN PRINT 2319 1775 Online 2320 7876

Research paper UGC CARE Listed (Group -I) Journal Volume 11, Iss 11, Nov 2022

[Accessed 12 November, 2015]

13. Mistry A, Stolnik S, Illum L., (2009). Nanoparticles for direct nose-to-brain delivery of drugs;379:146-157.
14. Kaur IP, Bhandari R, Bhandari S, Kakkar V., (2008). Potential of solid lipid nanoparticles in brain targeting. *J Control Release*;127(2):97-109.
15. Das NJ, Amiji MM, Bahia MF, Sarmento B., (2010). Nanotechnology-based systems for the treatment and prevention of HIV/AIDS. *Adv Drug Deliv Rev*.;62(4-5):458-477.
16. Gupta U, Jain NK., (2010). Non-polymeric nano-carriers in HIV/AIDS drug delivery and targeting. *Adv Drug Deliv Rev*.;62(4-5):478-490.
17. WHO. Safety of Efavirenz. 2010. [Online]. Available: http://www.who.int/hiv/topics/treatment/efavirenz_safety_review.pdf. [Accessed 12 November, 2015]
18. Bocedi A, Notaril S NP., (2004). Binding of anti- HIV drugs to human serum albumin. *Drug Metab Dispos*.:606-609.
19. Peroni RN, Di Gennaro SS, Hocht C, et al., (2011). Efavirenz is a substrate and in turn modulates the expression of the efflux transporter ABCG2/BCRP in the gastrointestinal tract of the rat. *Biochem Pharmacol*.;82(9):1227-1233.
20. Lembo D, Cavalli R., (2010). Nanoparticulate delivery systems for antiviral drugs. *Antivir Chem Chemother*.;21(2):53-70.
21. Varatharajan L, A TS., (2009). The transport of anti-HIV drugs across blood–CNS interfaces: Summary of current knowledge and recommendations for further research. *Antiviral Res*.;82(2):A99-A109.
22. Soto-Ramirez LE, Rodriguez-Diaz R, Harris DR, Hazra R., (2010). HIV drug resistance-associated mutations in antiretroviral na??ve HIV-1-infected Latin American children. *Adv Virol*.;2010.
23. Rausch DM, Stover ES., (2001). Neuroscience research in AIDS. *Prog Neuro-Psychopharmacology Biol Psychiatry*.;25(1):231-257.

ISSN PRINT 2319 1775 Online 2320 7876

Research paper UGC CARE Listed (Group -I) Journal Volume 11, Iss 11, Nov 2022

24. Mallipeddi R, Rohan LC., (2010). Progress in antiretroviral drug delivery using nanotechnology. *Int J Nanomedicine*. (1):533-547.
25. Date A., Destache CJ., (2013). A review of nanotechnological approaches for the prophylaxis of HIV/AIDS. *Biomaterials*.;34(26):6202-6228.
26. Kreuter J., (2014). Drug delivery to the central nervous system by polymeric nanoparticles: What do we know? *Adv Drug Deliv Rev*.;71:2-14.
27. Attama A, Momoh MA, (2012). Builders PF. Lipid Nanoparticulate Drug Delivery Systems: A Revolution in Dosage Form Design and Development. *Recent Adv Nov Drug Carr Syst*. 107-140.
28. Mehnert W, Mäder K., (2012). Solid lipid nanoparticles. *Adv Drug Deliv Rev*. ;64:83-101.
29. Blasi P, Giovagnoli S, Schoubben A, Ricci M, Rossi C., (2007). Solid lipid nanoparticles for targeted brain drug delivery. *Adv Drug Deliv Rev*.;59(6):454-477.
30. Füredi P, Kovács K, Ludányi K, Antal I, Klebovich I., (2016). Development and characterization of voriconazole loaded nanoparticles for parenteral delivery. *Int J Pharm*. ;510(1):159-163.
31. Blasi P, Giovagnoli S, Schoubben A, et al., (2011). Lipid nanoparticles for brain targeting I. Formulation optimization. *Int J Pharm*.;419(1-2):287-295.
32. Nowacek AS, McMillan J, Miller R, Anderson A, Rabinow B, Gendelman HE., (2010). Nanoformulated antiretroviral drug combinations extend drug release and antiretroviral responses in HIV-1-infected macrophages: Implications for NeuroAIDS therapeutics. *J Neuroimmune Pharmacol*.;5(4):592-601.
33. Galligioni V, Scagliarini A, Lorenzini L, et al. Nose-to-brain delivery of ribavirin (RBV) for the treatment of viral encephalitis.
34. WHO | HIV/AIDS. [Online]. Available: http://www.who.int/gho/hiv/en/. [Accessed 12 November, 2015.
35. Global HIV/AIDS Overview. [Online]. Available : https://www.aids.gov/federal-

ISSN PRINT 2319 1775 Online 2320 7876

Research paper UGC CARE Listed (Group -I) Journal Volume 11, Iss 11, Nov 2022

resources/around-the-world/global-aids-overview/. [Accessed 12 November, 2015]

36. Rao KS, Ghorpade A, Labhasetwar V., (2009). Targeting anti-HIV drugs to the CNS. *Expert Opin Drug Deliv*.;6(8):771-784.
37. Cundy KC, Lynch G, Lee WA.. (1997). Antiviral Research. 1997;35(2):113-122.
38. Hasegawa T, Kawaguchi T., (2002). Delivery of Anti-Viral Nucleoside Analogues to the Central Nervous System. *Curr Med Chem -Anti-Infective Agents*.;1(1):55-63.
39. Corbau R, Mori J, Phillips C, et al., (2010). Lersivirine, a nonnucleoside reverse transcriptase inhibitor with activity against drug-resistant human immunodeficiency virus type 1. *Antimicrob Agents Chemother*.;54(10):4451-4463.
40. Mistry A, Stolnik S, Illum L., (2009). Nanoparticles for direct nose-to-brain delivery of drugs;379:146-157.
41. Kaur IP, Bhandari R, Bhandari S, Kakkar V., (2008). Potential of solid lipid nanoparticles in brain targeting. *J Control Release*.;127(2):97-109.
42. Gupta U, Jain NK., (2010). Non-polymeric nano-carriers in HIV/AIDS drug delivery and targeting. *Adv Drug Deliv Rev*. ;62(4-5):478-490.
43. Naik A, Nair H., (2014). Formulation and Evaluation of Thermosensitive Biogels for Nose to Brain Delivery of Doxepin. *Biomed Res. Int.*;2014.1-10.
44. Michael J Pelczar, ECS Chan NRK. *Microbiology*., (1993). 5th ed. Tata Mc Graw Hill Publishing company Ltd.,New Delhi.
45. H.P. Rang, M.M.Dale, J.M. Ritter PKM. Pharmacology. In: *Pharmacology*. 5th ed. Churchill Livingstone; 2003:654-665.
46. Gelderblom HR. (1996). Structure and Classification of Viruses. In: Baron S, Medical Microbiology. 4th ed. Galveston (TX): University of Texas Medical Branch at Galveston.
47. Hynes M. Baltimore Classification of Viruses. *Mol Biol Webb*. 2015:1.
48. Retroviruses. [Online]. Available:http://retrovirology.biomedcentral.com/ [Accessed 12

ISSN PRINT 2319 1775 Online 2320 7876

Research paper UGC CARE Listed (Group -I) Journal Volume 11, Iss 11, Nov 2022

November, 2015]

49. Thakur DS, Behera CK, Patidar A, Kumar P, Kumar P, Lal C., (2010). Anti-HIV agents: A step towards future. *Int J Pharm Sci Rev Res*.;3(2):10-18.
50. Gupta U, Jain NK., (2010). Non-polymeric nano-carriers in HIV/AIDS drug delivery and targeting. *Adv Drug Deliv Rev*.;62(4-5):478-490.
51. Virus vs Retrovirus. [Online]. Available: http://www.differencebetween.com/difference-between-retrovirus-and-vs-virus/. [Accessed 25 June 2016]
52. Gupta U, Jain NK., (2010). Non-polymeric nano-carriers in HIV/AIDS drug delivery and targeting. *Adv Drug Deliv Rev*.;62(4-5):478-490.
53. Fisher, Bruce; Harvey, Richard P.; Champe PC. (2007). In: *Lippincott's Illustrated Reviews: Microbiology (Lippincott's Illustrated Reviews Series)*:3.
54. Chan DC, Fass D, Berger JM, Kim PS. , (1997) Core structure of gp41 from the HIV envelope glycoprotein. *Cell*.;89(2):263-273.
55. Foxall RB, Soares RS, Albuquerque AS, Cortesao CS, Victorino RMM, Sousa AE., (2008). Increased frequency of CD25dimCD4+ T-cells in HIV-2 infection, a naturally occurring attenuated form of HIV-1. *Clin Immunol*.;127(2):158-167.
56. List of Viral Diseases. [Online]. Available: http://doctors-hospitals-medical-cape-town-south-africa.blaauwberg.net/details.php ?id=768. [Accessed 25 June 2016]
57. Top 10 Deadliest Diseases in the world. [Online]. Available: https://www.microhealthllc.com/top-10-deadliest-diseases-in-the-world/ [Accessed 25 June 2016]
58. Overview of viral infections. [Online]. Available: http://www.merckmanuals.com/home/infections/viral-infections/overview-of-viral-inf

ISSN PRINT 2319 1775 Online 2320 7876

Research paper UGC CARE Listed (Group -I) Journal Volume 11, Iss 11, Nov 2022

ections. [Accessed 25 June 2016]

59. Alexander Krämer, Mirjam Kretzschmar KK., (2010). *Modern Infectious Disease Epidemiology Concepts, Methods, Mathematical Models, and Public Health*. New York: Springer.
60. William N. Rom SBM., (2007). *Environmental and Occupational Medicine*. 4th ed. Lippincott Williams & Wilkins.
61. Global HIV/AIDS Overview. https://www.aids.gov/federal-resources/around-the-world/global-aids-overview/. Accessed November 12, 2015.
62. WHO | HIV/AIDS. [Online]. Available: http://www.who.int/gho/hiv/en/. [Accessed November 12, 2015]
63. Lembo D, Cavalli R., (2010). Nanoparticulate delivery systems for antiviral drugs. *Antivir Chem Chemother*.;21(2):53-70.
64. FDA. FDA approved -HIV-Medicines. 2016. [Online]. Available: https://aidsinfo.nih.gov/education-materials/fact-sheets/21/58/fda-approved-hiv-medicines.[Accessed November 11, 2016].
65. Nelson AG, Zhang X, Ganapathi U, et al., (2015). Drug delivery strategies and systems for HIV/AIDS pre-exposure prophylaxis and treatment. *J Control Release*.;219(2015):669-680.
66. Hasegawa T, Kawaguchi T., (2002). Delivery of Anti-Viral Nucleoside Analogues to the Central Nervous System. *Curr Med Chem -Anti-Infective Agents*;1(1):55-63. 23.
67. Mallipeddi R, Rohan LC., (2010). Progress in antiretroviral drug delivery using nanotechnology. *Int J Nanomedicine*.;5(1):533-547.
68. Lun H, Chattopadhyay N, Yu X, Bendayan R., (2010). Nanotechnology applications for improved delivery of antiretroviral drugs to the brain.

ISSN PRINT 2319 1775 Online 2320 7876

Research paper UGC CARE Listed (Group -I) Journal Volume 11, Iss 11, Nov 2022

Adv Drug Deliv Rev. ;62(4-5):503-517.

69. Rao KS, Ghorpade A, Labhasetwar V.,(2009). Targeting anti-HIV drugs to the CNS. *Expert Opin Drug Deliv*.;6(8):771-784.
70. Cundy KC, Lynch G, Lee WA. Antiviral Research. 1997;35(2):113-122. doi:10.1016/j.antiviral.2009.11.004.
71. Dale Purves, George J Augustine, David Fitzpatrick, Lawrence C Katz, Anthony-Samuel LaMantia, James O McNamara and SMW, (2001). *Neuroscience*. 2nd ed. Sunderland (MA): Sinauer Associates.
72. Gizurarson S (2012). Anatomical and histological factors affecting intranasal drug and vaccine delivery. *Curr Drug Deliv*. 2012;9(6):566-582.
73. Pelvig DP, Pakkenberg H, Stark AK, Pakkenberg B. (2008). Neocortical glial cell numbers in human brains. *Neurobiol Aging*.;29(11):1754-1762.
74. Ginhoux F, Lim S, Hoeffel G, Low D, Huber T. (2013). Origin and differentiation of microglia. *Front Cell Neurosci*.;7(April):45.
75. Filiano AJ, Gadani SP, Kipnis J., (2014). Interactions of innate and adaptive immunity in brain development and function. *Brain Res*. 2015;1617:18-27.
76. GW K. The First Line of Defense in Brain Pathologies. (1995). *Drug Res (Stuttg)* ;45(1):357–360.
77. Krol S., (2012). Challenges in drug delivery to the brain: Nature is against us. *J Control Release*. 2012;164(2):145-155.
78. Gaillard PJ, Visser CC, Appeldoorn CCM, Rip J., (2012). Enhanced brain drug delivery: Safely crossing the blood-brain barrier. *Drug Discov Today Technol*.;9(2):e155-e160.
79. Wong HL, Wu XY, Bendayan R. (2012). Nanotechnological advances for the delivery of CNS therapeutics. *Adv Drug Deliv Rev*.;64(7):686-700.

ISSN PRINT 2319 1775 Online 2320 7876

Research paper UGC CARE Listed (Group -I) Journal Volume 11, Iss 11, Nov 2022

80. Chen Y, Liu L., (2012). Modern methods for delivery of drugs across the blood-brain barrier. *Adv Drug Deliv Rev*.;64(7):640-665.
81. Rausch DM, Stover ES., (2011). Neuroscience research in AIDS. *Prog Neuro-Psychopharmacology Biol Psychiatry*. 2001;25(1):231-257.
82. Park K. (2008). Trojan monocytes for improved drug delivery to the brain. *J Control Release*. ;132(2):75.
83. Varatharajan L, A TS., (2009). The transport of anti-HIV drugs across blood–CNS interfaces: Summary of current knowledge and recommendations for further research. *Antiviral Res*.;82(2):A99-A109.
84. Sozio P, Cerasa LS, Laserra S, et al., (2013). Memantine-sulfur containing antioxidant conjugates as potential prodrugs to improve the treatment of Alzheimer's disease. *Eur J Pharm Sci*.;49(2):187-198.
85. Perioli L, Ambrogi V, Bernardini C, et al., (2004). Potential prodrugs of non-steroidal anti-inflammatory agents for targeted drug delivery to the CNS. *Eur J Med Chem*. ;39(8):715-727.
86. Ikeda M, Bhattacharjee AK, Kondoh T, Nagashima T, Tamaki N (2002),. Synergistic effect of cold mannitol and Na(+)/Ca(2+) exchange blocker on blood-brain barrier opening. *Biochem Biophys Res Commun*.;291(3):669-674.
87. Qin LJ, Gu YT, Zhang H, Xue YX. (2009). Bradykinin-induced blood-tumor barrier opening is mediated by tumor necrosis factor-α. *Neurosci Lett*. 2009;450(2):172-175.
88. Hynynen K (2007). Focused ultrasound for blood – brain disruption and delivery of therapeutic molecules into the brain.:27-35.
89. Vykhodtseva N, McDannold N, Hynynen K., (2008). Progress and problems in the application of focused ultrasound for blood-brain barrier disruption.

ISSN PRINT 2319 1775 Online 2320 7876

Research paper UGC CARE Listed (Group -I) Journal Volume 11, Iss 11, Nov 2022

Ultrasonics;48(4):279-296.

90. Liu L, Guo K, Lu J, et al., (2008). Biologically active core/shell nanoparticles self-assembled from cholesterol-terminated PEG-TAT for drug delivery across the blood-brain barrier. *Biomaterials*;29(10):1509-1517.
91. Pang Z, Lu W, Gao H, et al., (2008). Preparation and brain delivery property of biodegradable polymersomes conjugated with OX26. *J Control Release*. 2008;128(2):120-127.
92. Rohit B, Pal KI., (2013). A Method to Prepare Solid Lipid Nanoparticles with Improved Entrapment Efficiency of Hydrophilic Drugs. *Curr Nanosci*.;9(2):211-220.
93. Delivery AD., (2009). Nanotechnology for Antiretroviral Drug Delivery. *J Am Chem Soc*.:21-23.
94. Bhanushali RS, Gatne MM, Gaikwad R V, Bajaj AN, Morde MA., (2015). Nanoemulsion based Intranasal Delivery of Antimigraine Drugs for Nose to Brain Targeting;71(6):707-709.
95. Mishra V, Kesharwani P., (2016). Dendrimer technologies for brain tumor. *Drug Discov Today*.;21(5):766-778.
96. Ingallina C, Rinaldi F, Bogni A, et al., (2016). Niosomal approach to brain delivery: Development, characterization and in vitro toxicological studies. *Int J Pharm*. ;511(2):969-982.
97. Kozlovskaya L, Stepensky D., (2013). Quantitative analysis of the brain-targeted delivery of drugs and model compounds using nano-delivery systems. *J Control Release*;171(1):17-23.
98. Van der Meel R, Vehmeijer LJC, Kok RJ, Storm G, van Gaal EVB., (2013). Ligand-targeted particulate nanomedicines undergoing clinical evaluation:

ISSN PRINT 2319 1775 Online 2320 7876

Research paper UGC CARE Listed (Group -I) Journal Volume 11, Iss 11, Nov 2022

Current status. *Adv Drug Deliv Rev*.;65(10):1284-1298.

99. Cundy KC, Lynch G, Lee WA.. (1997). Antiviral Research. 1997;35(2):113-122.

100. Hasegawa T, Kawaguchi T., (2002). Delivery of Anti-Viral Nucleoside Analogues to the Central Nervous System. *Curr Med Chem -Anti-Infective Agents*.;1(1):55-63.

101. Corbau R, Mori J, Phillips C, et al., (2010). Lersivirine, a nonnucleoside reverse transcriptase inhibitor with activity against drug-resistant human immunodeficiency virus type 1. *Antimicrob Agents Chemother*.;54(10):4451-4463.

102. Mistry A, Stolnik S, Illum L., (2009). Nanoparticles for direct nose-to-brain delivery of drugs;379:146-157.

103. Kaur IP, Bhandari R, Bhandari S, Kakkar V., (2008). Potential of solid lipid nanoparticles in brain targeting. *J Control Release*.;127(2):97-109.

104. Gupta U, Jain NK., (2010). Non-polymeric nano-carriers in HIV/AIDS drug delivery and targeting. *Adv Drug Deliv Rev*. ;62(4-5):478-490.

105. Naik A, Nair H., (2014). Formulation and Evaluation of Thermosensitive Biogels for Nose to Brain Delivery of Doxepin. *Biomed Res. Int.*;2014.1-10.

106. Chemical Products Corporation. (2012). GRAS Notice 000433: Generally Regarded as Safe (GRAS) determination notification for Poloxamer Fatty Acid Formulations;Poloxamer fatty acid esters: 1-36.

107. Corbau R, Mori J, Phillips C, et al., (2010). Lersivirine, a nonnucleoside reverse transcriptase inhibitor with activity against drug-resistant human immunodeficiency virus type 1. *Antimicrob Agents Chemother*.;54(10):4451-4463.

108. Mehnert W, Mäder K., (2012). Solid lipid nanoparticles. *Adv Drug Deliv Rev*. 2012;64:83-101.

109. Park JH, Ban SJ, Ahmed T, et al., (2015). Development of DH-I-180-3 loaded lipid nanoparticle for photodynamic therapy. *Int J Pharm*. 2015;491(1-2):393-401.

ISSN PRINT 2319 1775 Online 2320 7876

Research paper UGC CARE Listed (Group -I) Journal Volume 11, Iss 11, Nov 2022

110. Michael D. Triplett II BS., (2004). Enabling Solid Lipid Nanoparticle Drug Delivery Technology. Doctor of Philosophy dissertation. The Ohio State University.

111. Mallipeddi R, Rohan LC., (2010). Progress in antiretroviral drug delivery using nanotechnology. *Int J Nanomedicine*.;5(1):533-547.

112. Shegokar R, Singh KK, Müller RH., (2011). Production & stability of stavudine solid lipid nanoparticles - From lab to industrial scale. *Int J Pharm*.;416(2):461-470.

113. Kovacevic A, Savic S, Vuleta G, Müller RH, Keck CM., (2011). Polyhydroxy surfactants for the formulation of lipid nanoparticles (SLN and NLC): Effects on size, physical stability and particle matrix structure. *Int J Pharm*.;406(1-2):163-172.

114. Gupta U, Jain NK., (2010). Non-polymeric nano-carriers in HIV/AIDS drug delivery and targeting. *Adv Drug Deliv Rev*. ;62(4-5):478-490.