

Novel drug delivery approaches on antiviral and antiretroviral agents

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ABSTRACT

Viruses have the property to replicate very fast in host cell. It can attack any part of host cell. Therefore, the clinical efficacy of antiviral drugs and its bioavailability is more important concern taken into account to treat viral infections. The oral and parenteral routes of drug administration have several shortcomings, however, which could lead to the search for formulating better delivery systems. Now, a day's novel drug delivery systems (NDDS) proved to be a better approach to enhance the effectiveness of the antivirals and improve the patient compliance and decrease the adverse effect. The NDDS have reduced the dosing frequency and shorten the duration of treatment, thus, which could lead the treatment more cost-effective. The development of NDDS for antiviral and antiretroviral therapy aims to deliver the drug devoid of toxicity, with high compatibility and biodegradability, targeting the drug to specific sites for viral infection and in some instances it also avoid the first pass metabolism effect. This article aims to discuss the usefulness of novel delivery approaches of antiviral agents such as niosomes, microspheres, microemulsions, nanoparticles that are used in the treatment of various Herpes viruses and in human immunodeficiency virus (HIV) infections.

Key words: antiviral agents, herpes viruses, HIV, NDDS, viral infections

INTRODUCTION

Viruses are small (commonly range from 20 to 30 nm) obligate intracellular parasites consist of either double or single-stranded DNA or RNA enclosed in a protein coat called capsid. Antiviral agents are of two types, nonretroviral and retroviral drugs. Nonretroviral inhibitor acts on non-human immunodeficiency virus (HIV) infections. However, antiretroviral agents suppress the HIV replication, delay the onset of AIDS and prolongs patient's survival.

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According to Baltimore classification system,^[1] viruses are classified into families depending on their type of genome and their method of replication [Table 1].

Viral DNA enters into the host cell nucleus; further transcription of this viral DNA occurs into mRNA with the help of host cell RNA polymerase followed by translation of the mRNA into virus-specific proteins. The proteins formed contain some enzymes which aids in synthesizing more viral DNA as well as proteins of coat and envelope. On complete assembly of coat proteins around the viral DNA, virions are released by budding or after cell lysis.

Enzymes present in the virion synthesize its mRNA or the viral RNA serves as its own mRNA and translated into various enzymes, including RNA polymerase and structural proteins of the virion. After assembly, virions are released. There is no involvement of the host cell nucleus in replication of viruses.

The retrovirus virion consists of reverse transcriptase. This reverse transcriptase makes a DNA copy of the viral RNA. The DNA copy is then integrated into the genome of the host cell, which is termed as provirus and is transcribed into both new genomic RNA and mRNA for translation into viral proteins. The formed viruses are released by budding. HIV

is an RNA retrovirus. Some of the RNA retroviruses can also transform normal cells into malignant cells.^[2]

FORMULATION APPROACHES OF ANTI-VIRAL AND ANTIRETROVIRAL AGENTS

The global outlook for the development of novel drug delivery systems has been increasing day by day which results in formation of numerous innovative delivery systems for antiviral administration. The development of antiviral drugs can be hindered by several factors such as low efficacy of antiviral agents, less solubility of the compound, low bioavailability when administered in the form of conventional dosage form, some compounds have short half life, systemic toxic side-effects.

Taking into consideration above factors into account novel drug delivery approaches can be used to achieve efficacious therapy by improving the design, formulation and delivery of antiviral agents. An overview of the drug delivery systems most often studied for the use in antiviral and antiretroviral therapy has been given in Figure 1.

Eczema herpeticum also known as *Kaposi varicelliform* (described by Kaposi in 1887) is a disseminated viral infection characterized by fever, chills and malaise and clusters of itchy blisters or punched-out erosions. However, the complication in atopic dermatitis/eczema also results in eczema herpeticum. Most often eczema herpeticum are caused due to *Herpes simplex virus* type 1 or 2.^[3] It usually arises during a first episode of *Herpes simplex* infection (primary herpes). An antiviral drug acyclovir is used orally, or in the form of cream and ointment or by injection in the treatment of Eczema herpeticum.^[4]

Table 1: Classification of viruses on the basis of their method of replication

| Class | Method of replication | Example |
|-------|---|--|
| I | double- stranded DNA viruses | <i>Adenoviruses, Herpesviruses, Poxviruses</i> |
| II | single-stranded DNA viruses | <i>Parvoviruses</i> |
| III | double- stranded RNA viruses | <i>Reoviruses</i> |
| IV | single-stranded positive sense RNA viruses | <i>Picornaviruses, Togaviruses</i> |
| V | single-stranded negative sense RNA viruses | <i>Orthomyxoviruses, Rhabdoviruses</i> |
| VI | positive-sense single-stranded RNA viruses that replicate through a DNA intermediate | <i>Retroviruses</i> |
| VII | double-stranded DNA viruses that replicate through a single stranded RNA intermediate | <i>Hepadnaviruses</i> |

Orf is a virus infection of the skin contracted from sheep and goats is caused by a virus called the parapox virus of the family *Poxviridae*, which infects mainly young lambs and goats. Human lesions are caused via direct contact with the infected subject. The disease results in cutaneous pustular lesions, suggesting blood stream spread of the orf virus, but resolve within few weeks.^[5]

The large enveloped DNA virus of vertebrates belongs to the family *Herpesviridae*. This virus group has the property to establish latent infection and periodically reactivate. Human herpes viruses (HHV) include herpes simplex virus (HSV) type 1 and 2, Varicella-zoster virus (VZV), *Cytomegalovirus* (CMV), Epstein-Barr virus (EBV), and HHV-6, HHV-7 and HHV-8. HSV type 1 commonly associated with orofacial disease whereas HSV type 2 affects the genital area of humans. The most commonly anti viral drugs used for HSV infection are Acyclovir, Famcyclovir, Valcyclovir.^[6]

Another viral skin infection caused by Human Papilloma Virus (HPV) is known as viral warts. The viral warts are kind of benign proliferations of the skin and mucosa. The two vaccines, Gardasil[®], and Cervarix[®], has been approved by the Food and Drug Administration (FDA) in preventing persistent infections with regard to two HPV types that cause most cervical and anal cancers.^[7]

The causative agent of chicken pox is Varicella – zoster. Chicken pox is very highly contagious. The first sign of this disease is characterized by mild fever, weakness and rash. In 1995, a varicella vaccine (VARIVAX[®]) was licensed in the United States for people aged above 12 years. After that FDA approved acyclovir for varicella treatment in 1992.^[8]

Herpes zoster is also called as shingles characterized by painful eruption of small vesicles, or blisters, along the distribution area of the sensory nerves. Dormant Varicella

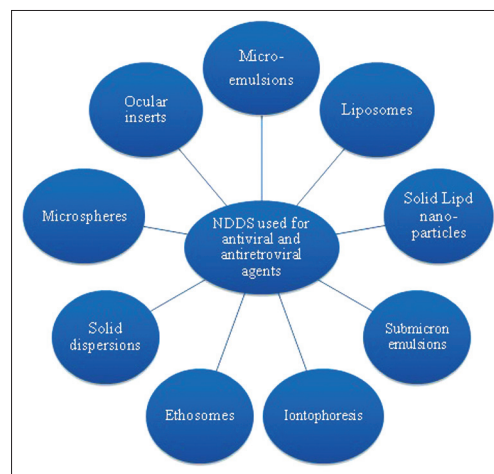


Figure 1: Schematic diagram of various drug delivery approaches used for antiviral and antiretroviral agents

zoster virus can cause shingles. The first vaccine approved by the FDA for adult shingles is known as Zostavax. Antiviral drugs like acyclovir, valaciclovir, famciclovir inhibits the viral replication and reduced the severity and duration of pain. HIV type 1 and type 2 also causes cutaneous manifestations. This is because HIV causes depletion of CD4+ cells, which is further initiated by an initial infection through Langerhans cells in mucosal tissue.^[9]

Recently, some novel approaches have been reported to treat above infection caused by different organism, in the form of the topical drug delivery system like transdermal drug delivery system. Transdermal drug delivery through the skin proves to be a convenient route of administration for variety of clinical manifestation.^[10] The main barrier of the skin is its outer most layer known as stratum corneum which prevents penetration of most of drugs through the skin. However, transdermal drug delivery or topical delivery possesses a number of significant advantages over more traditional dosage forms like reducing direct effects on the stomach and intestine, avoidance of first pass metabolism, patient compliance etc.^[11] The novel approaches which are used transdermally are colloidal systems, microparticulate system, nanodelivery systems, etc.

Microemulsions are thermodynamically stable dispersions of oil and water stabilized by a surfactant or by cosurfactant. Microemulsions enhance the bioavailability of poorly soluble antiviral and antiretroviral drugs such as acyclovir, penciclovir, ritonavir by maintaining them in molecular dispersion in the GI tract and hence, extend the absorption window available in the GI lumen.^[12,13]

Liposomes are the nanosized concentric bilayered vesicles in which aqueous volume is entirely enclosed by a membranous lipid bilayer mainly composed of natural and synthetic phospholipids. Ramana *et al.* prepared, a nevirapine-loaded liposomal formulation from egg phospholipids using thin film hydration showed maximum stability at physiological pH, prevent systemic toxic side-effects and enhance availability at targeted site.^[14]

On the other hand, solid lipid nanoparticles (SLN) also possess several benefits like their ability to protect chemically labile substances against chemical decomposition and their potential use in modulation of drug release.^[15] The SLN of adefovir dipivoxil were prepared by solvent diffusion method in an aqueous system and the results demonstrated that its inhibitory action *in vitro* was significantly increased.^[16] Atazanavir, HIV protease inhibitor (PI) exhibit low brain permeability. Therefore, to enhance brain uptake of atazanavir, the SLNs were prepared which showed promising drug delivery.^[17]

Another approach for antiviral and antiretroviral agents in the form of transdermal drug delivery includes

Iontophoresis technique, which leads to provide the penetration of hydrophilic and charged molecules across the skin. The antiviral therapy given by iontophoresis can provide the therapy in controlled fashion. Iontophoresis technique is capable of expanding the range of compounds that can be delivered through ocular, transungual, buccal or nasal route.^[18]

Ethosomes contain phospholipids, alcohol (ethanol and isopropyl alcohol) were reported to possess significantly higher transdermal flux of antiviral and antiretroviral agents. Ethosomes influenced the ultrastructure of stratum corneum which contributes in improving skin permeation of antiviral agents applied topically.^[19]

Different microspheres formulations have been studied as drug delivery systems for antivirals. Polymeric microspheres for topical application of acyclovir were formulated in order to increase the drug concentration in the basal epidermis (the site of HSV infections).^[20]

Ocular HSV type I cause infection of eye. It mainly affects the eyelids, conjunctiva, and cornea. Viral conjunctivitis known as pink eye refers to inflammation of conjunctiva. Viral conjunctivitis is caused due to adenoviruses.^[21] The different types of eye herpes are: herpes keratitis, stromal keratitis, Iridocyclitis. *Cytomegalovirus* retinitis is another eye infection if untreated leads to visual loss and blindness.

A various novel technologies are used in ocular delivery system to treat ocular viral infections like particulate formulations, colloidal formulations and some matrix types of system. Ocular drug delivery is a challenging task because of its numerous limitations like quick elimination from the precorneal area, solution drainage by gravity, induced lacrimation and normal tear turn over which results in poor bioavailability and produces systemic adverse effect from topically applied drugs. Novel technologies like Ocusert[®], Ocufit[®] SR, Minidisc, etc., are capable of reducing the systemic absorption of ocularly absorbed drug.^[22] Ocular inserts are biodegradable polymeric systems are being developed in order to attain better ocular bioavailability and sustained action of ocular drugs. Ocular inserts are the solid devices intended to be placed in the conjunctival sac and to deliver the drug at relatively slow rate.^[23] The ocular inserts of acyclovir were fabricated using two rate controlling biodegradable polymers i.e., hydroxypropyl methylcellulose and cellulose acetate phthalate (CAP) and dissolution rate of poorly soluble acyclovir was enhanced by β -cyclodextrin thus increasing the efficacy of hydrophobic drug which gets poorly absorbed through cornea.^[22]

Humans possess retroviruses exist in two forms: as normal genetic elements in their chromosomal DNA (endogenous retroviruses) and as horizontally transmitted infectious

RNA-containing viruses which are transmitted from human to human (exogenous retroviruses, e.g., HIV and human T-cell leukemia virus, HTLV).

Infection with HIV results in AIDS. The WHO estimates about more than 25 million people worldwide have been died due to AIDS and in 2008 approximately 33.4 million people including 2.1 million children under age 15 were infected with AIDS. HIV possesses enzyme reverse transcriptase consist of lipid bilayer membrane surrounding the capsid. Its surface glycoprotein binds to CD4 receptors and to chemokine coreceptor on the T-cell. After penetrating the host cell, the virus sheds its outer coat and releases its genetic material. Over a prolonged period the T-helper cell depleted from the body. The normal range of CD4-positive T-lymphocytes vary between 500 and 1500 cells/mm³ in blood. HIV consists of an external lipid bilayer glycoprotein envelope (including envelope proteins gp 120 and gp 41), an internal protein core (proteins p15, p17, and p24), a viral RNA complexed with reverse transcriptase. The HIV genome is approximately 10 kilobases, which is larger than that of HTLV. HIV is classified as a retrovirus because it contains reverse transcriptase. It is a D-type virus in the *Lentivirus* family. Infection of cultured T4 cells with HIV usually results in cell death.^[24,25]

HTLVs are members of the *Oncovirus* family of retroviruses, which are distinguished from other viruses by the presence of reverse transcriptase, an enzyme that transcribes RNA into DNA. Tax and rex, are the two genes possessed by HTLVs required for viral replication and efficient transcription of the HTLV genome. Three types of HTLV are recognized: HTLV-1, HTLV-2, and HTLV-5 HTLVs. These are classified on the basis of two factors; first isolation from and ability to infect mature T-cells and second are the presence of reverse transcriptase and cross-reacting internal core proteins. Infection with HTLV-1 cause immunosuppression, alters helper T-cell function by causing increased proliferation and induces nonspecific polyclonal immunoglobulin production by B cells regardless of the type of antigen-presenting cell. One unique characteristic of HTLV-1 infection is the extremely long incubation period between initial infection and the occurrence of disease.^[26]

Controlling HIV infections some novel approaches have been utilized in the form of solid dispersions and cationic submicron emulsion. Among various approaches solid dispersions can be used to improve the dissolution of BSC Class II drugs due to particle size reduction, increased wettability because of use of hydrophilic carriers and increased surface area.^[27] It has been reported that dissolution of antiretroviral agents can be enhanced by solid dispersion technique.^[28] Submicron emulsions are the drug carriers for both lipophilic and amphiphilic drugs consists of many favorable properties such as biocompatible, biodegradable, stable and easy to prepare. Submicron

emulsion of antiretroviral drug indinavir has been prepared to target the drug at the specific site thereby improving its therapeutic index.^[29]

Taking above information in view this article summarize some novel approaches that have been reported with respect to different antiviral and antiretroviral agents.

ANTIVIRAL DRUGS

Anti-herpes Virus

Idoxuridine

Idoxuridine (5-iodo-2'-deoxyuridine) is an iodinated thymidine analog that inhibits the *in vitro* replication of various DNA viruses, including herpes viruses and pox viruses.^[30]

In the U.S., idoxuridine is approved only for topical treatment of HSV keratitis for topical treatment of herpes labialis, genitalis, and zoster. In ocular HSV infections, topical idoxuridine is more effective in epithelial than in stromal infections.

Topical liposomal gel of idoxuridine was prepared by Seth *et al.*^[31] by reverse phase evaporation method. The antiviral efficacies of topical liposomal gel compared with plain liposomes were tested. The result demonstrated that IDU liposomes gel has improved therapeutic efficacy in treatment of HSV-1 and HSV-2 infections. Also it has shown more drug retention to the skin due to its entrapment in the liposomal vesicles than the plain liposomes.

In another study, the idoxuridine was incorporated in the glycyrrhizin gel as topical preparation.^[32] Glycyrrhizin is a triterpenoidsaponin and is a chief constituent of liquorice.^[33] The idoxuridine containing glycyrrhizin gel was then compared with a commercial IDU ointment (Virusan) at two temperatures on intact and stripped skin *in vitro*. The results demonstrated that at 34°C the normalized flux (Fn) values of IDU glycyrrhizin gel were six times higher than Virusan when tested on intact hairless mouse skin. At 25°C, Fn values were 22 and 25 times greater for the gel formulation using intact and stripped skin, respectively. By these *in vitro* results, it was concluded that IDU penetrates the skin more effectively when incorporated in the glycyrrhizin gel than in the ointment.

Acyclovir is an acyclic guanine nucleoside analog that lacks a 3'-hydroxyl on the side chain.^[34] Valacyclovir is the L-valyl ester prodrug of acyclovir.^[35]

Acyclovir is most active against HSV-1, approximately half as active against HSV-2, a tenth as potent against *Varicella-zoster virus* (VZV) and *Epstein-Barr virus* (EBV), and least active against *Cytomegalovirus* (CMV) and human herpes virus (HHV-6). Oral valacyclovir is as effective as oral

acyclovir in HSV infections and more effective for treating *Herpes zoster*.^[36,37]

Acyclovir is also available topically in the form of cream but problem associated with this marketed formulation is its poor penetration through the stratum corneum and thus restricts the movement of sufficient drug due to which the cream should be applied five times a day so that the required amount of drug get available to the basal epidermis.

So to overcome the penetration problem attempts have been made to develop a therapeutically effective topical delivery system of acyclovir in the form of microemulsions.^[38]

Microemulsion has a property of improve drug stability and availability because of surfactant solubilization of the drug. Different batches of microemulsion were prepared using eucalyptol, transcutool, and peppermint oil of various strengths i.e., 1%, 2.5%, 5% as penetration enhancers. The oily phase and aqueous phase consist of isopropyl myristate and water /dimethylsulfoxide (1:3), respectively. Using tween20 as surfactant in water phase and span80 as cosurfactant in oil phase; acyclovir water-in-oil microemulsions were prepared. The *in vitro* skin permeation test was done through laca mice skin using Franz diffusion cell and *in vivo* studies were performed using female Balb/c mice. The results concluded that batch T-2 microemulsion which contains 2.5% transcutool (penetration enhancer) has 1.7-fold enhancement in flux and permeation coefficient as compared to marketed cream and PEG ointment. Also it has been observed that single application of 2.5% transcutool microemulsion was more effective in the treatment of herpetic skin lesions.

Chetoni *et al.* compared positively charged liposome-encapsulated acyclovir (ACV) with commercial acyclovir ointment for ocular delivery.^[39] In this study, the pharmacokinetic profile of the drug in the aqueous humor of rabbits after topical administration was determined. The applied dose of ACV was 0.18 mg, except for the full-strength (3.0 %) ointment, in which case it was 1.5 mg. The aqueous humor ACV concentration maintained by LIPO-ACV during the plateau was in the upper range of the ID (50) s (0.01 to 0.7 µg/mL) reported for *Herpes simplex* type 1. On the other hand, in spite of the much higher dose (1.5 versus 0.18 mg), the area under curve (AUC) produced by the full-strength 3.0 % ointment was only 1.6 times greater than that corresponding to the liposomal vehicle. Topical delivery of ACV can be improved by iontophoresis. By this technique, the delivery of ACV resulted in high drug levels in skin layers to form a drug depot, which persisted over 2-3 days.^[40]

Another study revealed that a water-soluble ester of acyclovir i.e. 2'-O-glycylacyclovir used for topical treatment of experimental herpes simplex keratouveitis. It has been

proved efficacious in the topical treatment of epithelial and stromal herpes simplex keratitis, and iritis therewith associated, when administered as a 1% eyedrop formulation to rabbits.^[41]

However, the novel drug delivery systems like ocular inserts and biodegradable polymeric systems etc., has been proved to be successful and beneficial to attain improved bioavailability and sustained action of ocular drugs. Taking above information in view attempts have been made to prepare polymeric ocular delivery of acyclovir.^[42] Ocular inserts are solid devices, placed in the conjunctiva sac and deliver the drug in controlled fashion. The polymeric drug reservoir cast films were prepared by dissolving 1% w/v, 1.5% w/v and 2% w/v of hydroxyl propyl methyl cellulose (HPMC-K₄M) in 15 ml double distilled water. Incorporated ACV-β-CD solution (dissolved in 10 ml 0.1N NaOH) into the polymer solution. PEG-400 was used as plasticizer and penetration enhancer. HPMC containing acyclovir matrix film was enclosed in two rate controlling membranes of cellulose acetate phthalate (CAP). The *in vitro* drug release studies showed prolonged and constant release rate upto 20 hour with nonfickian diffusion behavior. The batches which contain 5% w/v CAP reported maximum cumulative release of 98%. *In vivo* release of the drug were conducted on the rabbit eye demonstrated that the optimized batches consists of 1.5% w/v and 2.0% w/v HPMC-K₄M, respectively.

Cutaneous delivery of acyclovir can be improved by using topical iontophoresis of valacyclovir hydrochloride.^[43] Valacyclovir is a prodrug of acyclovir and enhanced the dermal and transdermal delivery of drugs with unfavorable partition coefficients. Due to charged nature, it gets more efficiently iontophoresed into the skin in comparison to acyclovir (parent molecule). The *in vitro* experiment was conducted using porcine skin and the cumulative permeation of ACV showed efficacious result after VCV iontophoresis.

Cidofovir

Cidofovir (1-[(S)-3-hydroxy-2-(phosphonomethoxy)-propyl] cytosinedihydrate) is a cytidine nucleotide analog with inhibitory activity against human herpes, papilloma, polyoma, pox and adenoviruses.^[30]

Cidofovir 1%, with and without cyclosporin A 1% as a topical treatment of acute adenoviral keratoconjunctivitis was studied, it was seen that cidofovir ($P=0.048$) lowers the frequency of severe corneal opacities, but its clinical use 4 to 10 times daily at a 1% concentration causes local toxicity.^[44]

Attempts have been made to use Cidofovir in acyclovir-resistant herpes infection. In one study, done by Martinez CM *et al.*,^[45] it was found that acyclovir resistant strains became sensitive to cidofovir therapy. The intravenous formulation of cidofovir is commercially available and requires

weekly dosing and is efficacious. Disadvantages include the complexity of administration and the adverse effect profile. Nephrotoxicity is the main dose limiting side effect of intravenous cidofovir. The topical formulation of cidofovir is better for mucocutaneous HSV infection because it is usually undetectable in the blood further its topical application leads to patient compliance. Therefore, systemic adverse effects should also be minimized.

Orf is a viral disease that is widespread in sheep and goats. Orf can be transmitted to humans by contact with an infected animal or contaminated fomites. Keeping in view of this orf virus Sonvico *et al.*^[46] has described the therapeutic paint of cidofovir/sucalfate gel which is used in combination and administered topically by spraying for treatment of orf virus infections. Sucalfate gel is bioadhesive in nature, therefore, it is used in combination with an antiviral drug; cidofovir for maintaining contact time between the drug and the lesion. Spray formulations of different strengths containing sucalfate (15% w/w), cidofovir (0.5%w/w or 1%w/w), sodium dihydrogen phosphate (6%, 11% or 16% w/w) were prepared. Cidofovir 1%w/w in Beeler base cream was taken as reference. *In vitro* release was studied using Franz diffusion cells equipped with dialysis tubing membrane as a barrier. *In vitro* results suggested that the transport rate of cidofovir was more in the sucalfate/phosphate/cidofovir formulation than in the semisolid formulation (Beeler base cream). *In vivo* studies were done on lambs infected with orf virus demonstrated the efficacious use of therapeutic paint.

Famciclovir and Penciclovir

Famciclovir is a diacetyl ester prodrug of 6-deoxy penciclovir. Penciclovir(9-[4-hydroxy-3-hydroxymethylbut-1-yl] guanine) is an acyclic guanine nucleoside analog.^[47]

Famciclovir inhibits *H. simplex*, *H. zoster* but not acyclovir resistant strains.^[48]

It is converted into penciclovir in two steps. The first-step process occurs in the gut and the second occur in the liver.^[49]

It has been reported that microemulsion-based hydrogel formulation of penciclovir could be a promising vehicle for topical delivery of penciclovir. Permeation test *in vivo* was done in mice showed that compared with the commercial cream, microemulsion-based hydrogel and microemulsion could significantly increase the permeation of penciclovir into both epidermis and dermis. A microstructure change of skins was observed after administration under light microscope and scanning electron microscope (SEM). These changes might occur due to the interaction of the ingredients of microemulsion with skins, which was related with the permeation enhancement of penciclovir.^[50]

Microemulsion of penciclovir was also prepared for dermal

delivery.^[51] There are several advantages of preparing microemulsion for dermal delivery of drugs like increased concentration of skin, increased thermodynamic activity of drug which, in turn, increases its partitioning into the skin. Another most important advantage is that the ingredients present in the microemulsion-like penetration enhancers reduces the diffusional barrier of the stratum corneum and increase permeation rate of drug into the skin.^[52] A study investigated microemulsion for delivering penciclovir topically. It was concluded that the permeability of penciclovir was significantly increased from the microemulsion formulation compared with commercial cream. The physicochemical properties of the optimized microemulsion and the permeating ability of penciclovir from microemulsions were also investigated and the results showed that the optimized microemulsion formulation was composed of oleic acid (5%, w/w), Cremophor EL (20%, w/w), ethanol (30%, w/w) and water (45%, w/w). And the cumulative amount of penciclovir permeated through excised mouse skins from microemulsion was about 3.5 times that of the commercial cream.

For topical treatment of penciclovir, solid lipid nanoparticles also possess a satisfactory approach which enhances skin penetration of the drug. Solid lipid nanoparticles (SLNs) are colloidal carrier systems composed of physiological and biodegradable lipids of low toxicity.^[53] Its enhanced skin penetration is thought to be due to an occlusive properties i.e., an increase in skin hydration caused by the occlusive film formed on the skin surface by the SLN.^[10]

A solid lipid nanoparticle incorporating penciclovir were prepared by a double (W/O/W) emulsion technique. The SLNs prepared were spherical in shape having a mean diameter of 254.9 nm and entrapment efficiency of 92.40%. Permeability studied through excised rat skin revealed that cumulative amount of drug penetrated was more 2-fold from SLNs compared with that of commercial cream as a control at 12 h after administration. Interaction between SLNs and the skin surface were seen microscopically showed that the SLNs changed the apparent morphology of stratum corneum and broke the close conjugation of corneocyte layers, which was the possible reason that SLNs increased the permeation of penciclovir into skin dermis.^[54]

Effect of famciclovir on Herpes simplex virus Type 1 corneal disease and establishment of latency in rabbits has been reported by Loutsch *et al.*^[55] Famciclovir was administered orally to treat ocular herpes infection in rabbits and comparison was made with that of topically used trifluorothymidine (treatment of choice for Herpes keratitis). The virus used in this study was HSV-1 strain 17syn+. The results indicated that the oral famciclovir when administered twice a day in a dose- dependent manner (60- 500 mg/kg body weight), improves the herpes keratitis SLE scores. The efficacy of oral famciclovir 250 mg/kg compared with

that of topical drops of 1% trifluorothymidine (TFT). It was seen that the rabbits that received FCV had a significant increase in the rate of survival compared to that of rabbits that received TFT. This occurs due to the fact that, although TFT treatment was more effective in reducing eye diseases but the FCV treatment reduced the severity of corneal infections i.e., reduces the number of HSV-1 genomes in the trigeminal ganglia of latently infected rabbits, hence improves survival.

Foscarnet

Foscarnet (trisodiumphosphonoformate) is an inorganic pyrophosphate analog that inhibits herpesviruses and HIV. It selectively inhibits the DNA polymerase of human herpes viruses, including cytomegalovirus and the reverse transcriptase of HIV, thereby, inhibiting their replication. Intravenous foscarnet is effective for treatment of CMV retinitis, including ganciclovir-resistant infections, other types of CMV infection, and acyclovir-resistant HSV and VZV infections. Most common dose-limiting side effect associated with foscarnet is nephrotoxicity which can be minimized by the dosage adjustment of foscarnet depending on the serum creatinine level, using intermittent rather than continuous infusions, providing adequate prehydration and avoiding other potentially nephrotoxic drugs.^[56]

Oral bioavailability of foscarnet is low i.e., it is poorly absorbed through GIT [Table 2] and may cause gastrointestinal disturbances. The use of a gel formulation containing combinations of foscarnet and SLS (sodium lauryl sulfate) has been studied by Piret *et al.* and this could represent an attractive approach for the treatment of herpetic mucocutaneous infections. The formulation was evaluated using a murine model of orofacial infection. Gel was applied topically twice a day for 3 days and was initiated at 6, 24, 48 hour after virus inoculation. The results demonstrated that the gel formulation that contained both 3% foscarnet and 5% SLS and that was administered within 48 hour postinfection reduced the rate of development of herpetic skin lesions. However, this formulation when administered within 24 and 6-hour postinfection decreased the viral content in skin tissues and in ipsilateral trigeminal ganglia, respectively. On the other hand, less efficacious results have been showed by gel formulation containing 3% foscarnet alone.^[57]

Considering that sodium lauryl sulfate (SLS), a skin penetration enhancer, and also a potent inhibitor of various HIV strains Piret *et al.* also studied the effect of SLS on a topical formulation of Foscarnet against HSV Type 1 cutaneous lesions in mice.^[58]

Topical preparation of 3% Foscarnet cream was evaluated with efficacy for treatment of Herpes labialis.^[59] An experimental studies was done on healthy adult human volunteer, have a history of sunlight-induced Herpes labialis. Lips of these subjects were then exposed to ultra

violet light and immediately after exposure, cream was applied approximately eight times daily for 7 days. The results showed that the foscarnet cream significantly reduced the mean lesion area and maximum lesion area. The time of healing of delayed classic lesions was also got reduced. Also no significant adverse effects were observed by the use of this cream.

Ganciclovir and Valganciclovir

Ganciclovir (9-[1, 3-dihydroxy-2-propoxymethyl] guanine) is an acyclic guanine nucleoside analog that is similar in structure to acyclovir except for an additional hydroxymethyl group on the side chain.^[60]

Ganciclovir was first synthesized by Julien Verheyden and John Martin at Syntex Research in California in 1980. Ganciclovir sodium possesses marketed formulation under the trade names Cytovene and Cymevene (Roche). For ocular use ganciclovir is marketed under the trade name Vitrasert (Bausch & Lomb). Valganciclovir is the L-valyl ester prodrug of ganciclovir with improved oral bioavailability. It shows inhibitory activity against all Herpes viruses but is especially active against CMV and have high adverse effect of causing myelotoxicity in clinical use.^[61]

Ganciclovir is a broad-spectrum virustatic agent. Ganciclovir ophthalmic gel in two different strengths of 0.05% and 0.15% were compared with 3% acyclovir ointment in the treatment of superficial herpes simplex keratitis in humans. The results were concluded on the basis of clinical trials which were carried out in patients in Africa and Europe, named Trial 1 and Trial 2, respectively. The study showed no statistically significant difference between the treatment groups, although the healing rates were found to be better in the group receiving 0.15% ganciclovir gel, with healing rates of 85% (Trial 1) and 83% (Trial 2) as compared with 72% (Trial 1) and 71% (Trial 2) in the group receiving acyclovir ointment. Systemic absorption of the drug was low. Hence, this study supported the efficacious use of Ganciclovir ophthalmic gel (Virgan; 0.15%) in the treatment of herpes simplex keratitis.^[62]

Herrero *et al.* prepared biodegradable poly (DL-lactide-co-glycolide) (PLGA) loaded ganciclovir microspheres for intraocular administration using a dispersion of ganciclovir in fluorosilicone oil (FSiO), which was further dispersed in an acetone solution of PLGA [50/50 and inherent viscosity 0.41 dL/gm], and emulsified in silicone oil with a surfactant and sterilized. This preparation technique described resulted in high ganciclovir loading (95%) and prolonged drug release. The ganciclovir formulation behaved similarly before and after the sterilization process.^[63]

The ganciclovir implant was prepared for sustained-release intraocular drug delivery system to treat cytomegalovirus

Table 2: Physicochemical, biopharmaceutical characteristics and marketed formulations of antiviral agents

| S.no. | Name | Solubility (mg/ml) | t _{1/2} (hr) | Log P | Protein binding (%) | Brand name |
|-------|-------------------------------|------------------------------|-----------------------|-------|---------------------|---|
| 1. | Anti-Herpes virus | | | | | |
| | Idoxuridine | 1.6 | 0.5 | -0.53 | N/A | Herplex |
| | Acyclovir | 2.5 | 2.5-3.5 | -1.56 | 9-33 | Zovirax (Sodium salt), xerese (hydrocortisone salt) |
| | Valacyclovir | 70 | 2.5-5.3 | -0.3 | 13-18 | Valtrex (Hydrochloride salt) |
| | Famciclovir | 25 | 10 | 0.6 | 20-25 | Famvir |
| | Penciclovir | | 2 | -1.1 | 20 | |
| | Ganciclovir | 2.6 | 2-4 | -1.7 | 1-2 | Vitrasert, Zirgan; and cytovene-IV (Sodium salt) |
| | Foscarnet | 1.68 | 3.3-6.8 | -2.1 | 14-17 | Foscavir (Sodium salt) |
| 2. | Anti - retrovirus | | | | | |
| | Zidovudine | 20.1 | .5-3 | 0.05 | 30-38 | Retrovir |
| | Didanosine | 27.3 | 0.5 | -0.2 | <5 | Videx EC |
| | Zalcitabine | 76.4 | 2 | -1.3 | <4 | Hivid |
| | Stavudine | 83 | 0.8-1.5 | -0.8 | Negligible | Zerit |
| | Lamivudine | 70 | 5-7 | -1.4 | 36 | Epivir |
| | Abacavir | 77 | 1.54±0.63 | 1.1 | Approx 50 | Ziagen (Sulfate salt) |
| | Nevirapine | 0.007 | 45 | 1.75 | 60 | Viramune |
| | Efavirenz | <.001 | 40-55 | 4.6 | 99.5-99.75 | Sustiva |
| | Delavirdine | 0.2942 | 5.8 | 2.8 | 98 | Rescriptor (Mesylate salt) |
| | Ritonavir | 1.26 | 3-5 | 3.9 | 98-99 | Norvir |
| | Amprenavir | 0.04 | 7.1-10.6 | 2.43 | 90 | Agenerase |
| | Lopinavir | 1.92 | 5-6 | 4.69 | 98-99 | Kaletra |
| 3. | Anti-Influenza virus | | | | | |
| | Amantadine | 6.2 | 10-14 | 2.3 | Approx 67 | Symmetrel (Hydrochloride salt) |
| | Rimantadine | 50 | 25-30 | 3.6 | Approx 40 | Flumadine (Hydrochloride salt) |
| 4. | Non selective antiviral drugs | | | | | |
| | Ribavirin | 142 | 9.5 | -2.6 | N/A | Copegus, rebetol, virazole |
| | Adefovir dipivoxil | 19 at pH2.0; 0.4 at pH7.2 | 7.48±1.65 | 0.8 | ≤4 | Hepsera |

retinitis. A high and steady-state concentration of the drug in the vitreous cavity over a period of 7-8 months was observed. Randomized, controlled clinical trials have demonstrated a superior efficacy of the implant compared with intravenous ganciclovir. But the severe adverse effects associated with the implant are blinding, provides no protection against second-eye or visceral cytomegalovirus retinitis infections. This review summarizes the clinical indications for and complications associated with the ganciclovir implant.^[64]

Antiretrovirus

A retrovirus is an RNA virus that is duplicated in a host cell using the reverse transcriptase enzyme to produce DNA from its RNA genome. With the help of integrase enzyme the DNA gets incorporated into the host's genome. The virus thereafter replicates as part of the host cell's DNA. Retroviruses are enveloped viruses that belong to the viral family *Retroviridae*. The retroviral nucleocapsid is the inner structure of the virus where several hundred nucleocapsid

protein (NC) molecules coat the dimeric, genomic RNA. The NC was found to play multiple roles in the viral life cycle during the copying of the genomic RNA into the proviral DNA by viral reverse transcriptase and integrase, and is therefore considered to be a prime target for anti-HIV therapy.^[65]

Class- I Nucleoside Reverse Transcriptase Inhibitors (NRTIs)

NRTIs, sometimes also called "nucleoside analogues" or "nukes", that contain faulty versions of the building blocks (nucleotides) used by reverse transcriptase to convert RNA to DNA. This class inhibits activity of reverse transcriptase, which is reproduced by HIV. When reverse transcriptase uses these faulty building blocks, the new DNA cannot be built correctly and hence, its proliferation in the body is halted.^[66]

The first antiretroviral drug developed in 1987 i.e., Zidovudine.^[67]

Zidovudine

Zidovudine is a synthetic thymidine analog with potent activity against a broad spectrum of retroviruses including HIV-1, HIV-2, and human T-cell lymphotropic viruses (HTLV) I and II.

A novel targeted sustained drug delivery of Zidovudine was prepared in the form of emulsomes thereby reducing its toxicity due to localization of drug into the liver. Emulsomes are the lipoidal vesicular system with an internal solid fat core surrounded by a phospholipid bilayer. Zidovudine emulsomes contained phosphatidyl choline, cholesterol and either of the solid lipids tristearin or trilaurin in different molar ratios. Stearylamine was also incorporated to impart cationic charge to the system. The cationic charge prevents lysosomal degradation and ensures the intracellular localization of the system, with subsequent slow release of zidovudine from the internal solid core, and thereby might overcome the problem of multidrug resistance. The study indicates that maximum entrapment efficiency obtained from trilaurin and tristearin were $53.7 \pm 5.5\%$ and $55.3\% \pm 5.8\%$, respectively, having solid lipid-cholesterol- phosphatidyl choline mole ratio of 1:0.5:1. Further addition of cationic-charge i.e., stearylamine also resulted in increase in entrapment efficiency. The optimum mole ratio of solid lipid-cholesterol-phosphatidylcholine-stearylamine was found to be 1:0.5:1:0.1, at which entrapment efficiencies of $57.8 \pm 6.2\%$ and $59.7 \pm 6.1\%$, respectively, and mean particle size of 130 ± 18 and 142 ± 22 nm were found for the trilaurin- and tristearin-based formulations, respectively. *In vivo* organ distribution studies were done on albino rats (100-150 g) demonstrated better uptake of emulsomal formulations by the liver cells. Further, a significantly higher ($P < 0.05$) liver concentration of drug was estimated over a period of 24 hour for cationic emulsomes than for plain neutral emulsomes. Cationic emulsomes reduces the toxicity problem due to favorable localization of the drug in liver cells, it could fuse with the endosomal membrane due to charge-charge interaction and were released in the cytoplasm before lysosomal degradation and could sustain drug release over a prolonged period. The proposed cationic emulsome-based system showed excellent potential for intracellular hepatic targeting and the strategy could play a vital role in the effective treatment of life-threatening viral infections, such as hepatitis, HIV and Epstein-Barr virus infection.^[68]

Zalcitabine

Zalcitabine is a dideoxynucleoside compound in which the 3'-hydroxyl group on the sugar moiety has been replaced by hydrogen. This modification prevents the formation of 5' to 3' phosphodiester linkages, which are necessary for the elongation of DNA chains, thus resulting in the termination of viral DNA growth. It is a potent inhibitor of HIV replication at low concentrations, acting as a chain-terminator of viral DNA by binding to reverse transcriptase.

Its main toxic side effect is axonal degeneration resulting in peripheral neuropathy.^[69]

An experiment on transdermal preparation of zalcitabine was studied by Kim *et al.* The objective of this study was to maintain blood concentration of drug within therapeutic range for longer duration and also to reduce side effect caused due to high-dose administration. Different permeation enhancers were used to increase penetration of drug into the skin. *In vitro* skin permeation was done on freshly excised hairless rat skin and human cadaver skin at 37°C. The result demonstrated that the addition of 1% v/v oleic acid in ethanol/water (60:40) cosolvent system enhanced the skin permeation rate of drug with reduced lag time. This enhancement is due to the synergistic effect of oleic acid and ethanol to make transdermal delivery of zalcitabine feasible.^[70]

Stavudine

Stavudine is a synthetic thymidine nucleoside analog, active against the HIV type 1 (HIV-1). The chemical name for stavudine is 2',3'-didehydro-3'-deoxythymidine.^[71]

It was observed that the cidofovir used in ophthalmological nosocomial infections caused by adenovirus may obstruct the lacrimal duct when used locally. Considering this in mind Inoue *et al.* reported the antiadenoviral activity of zalcitabine and stavudine. Cidofovir, zalcitabine and stavudine 1% solutions and balanced salt solution were given as eye drop to healthy female Japanese albino rabbits 4 times a day for 14 days. The results showed that zalcitabine and stavudine did not induce any change in lacrimal pathway.^[72]

A methoxypoly (ethylene glycol) carbonate derivative of stavudine was synthesized to formulate transdermal delivery of stavudine. Synthesis of carbonates were done in a two-step process by coupling the methoxypoly (ethylene glycol) promoiety of various chain lengths to C-5' of stavudine. The aqueous solubility was increased on lengthening of the ethylene oxide side chain, although, there was no significant increase in the estimated solubility of octanol. However, *in vitro* results suggested that the most effective penetrant, the derivative with three ethylene oxide units in side chain, exhibited a flux of 26.1 nmol/cm²/h as compared to 59.15 nmol/cm²/h of the parent stavudine. Hence, no permeation enhancement was seen during this study.^[73]

The outermost layer of the skin i.e., the stratum corneum acts as the main barrier for penetration of the drugs. The transdermal penetration depends upon various factors like aqueous solubility of drug, molecular size, partition coefficient, alkyl chain length, etc. different ester groups in 5' position of stavudine was synthesized and its effect on transdermal penetration with or without the use of

Pheroid™ as delivery system was studied. Pheroid™ is a patented system consists unique submicron emulsion type formulation (200-440 nm), capable of encapsulating a variety of drugs and delivering these drugs with high efficacy to target sites within the body. Vertical Franz diffusion cells were used for skin penetration studies. The transdermal flux of stavudine (6.52 $\mu\text{mol}/\text{cm}^2\cdot\text{h}$) in phosphate buffer solution pH 7.4 was much higher as compared to its derivatives named stavudine-5'-Hexanoate, butyrate, propionate, acetate which has a flux of 0.06, 0.17, 0.21, 0.23 $\mu\text{mol}/\text{cm}^2\cdot\text{hour}$, respectively. On the other hand with Pheroid™, propionyl and butyryl esters showed the highest transdermal flux of 6.64 and 6.87 $\mu\text{mol}/\text{cm}^2\cdot\text{hour}$, respectively. Depending on physicochemical properties and alkyl chain length it was concluded that the esterification of stavudine results in higher partition coefficient and lowest aqueous solubility.^[11]

Lamivudine

Lamivudine[(-)2', 3'-dideoxy, 3'-thiacytidine, 3TC] is a cytosine analog reverse transcriptase inhibitor that is active against HIV-1, HIV-2, and HBV. Lamivudine is one of the least toxic antiretroviral drugs, generally well tolerated and has few adverse effects.

Ethosomes prepared for transdermal drug delivery influenced the ultrastructure of stratum corneum and thus improves skin permeation. Both ethosomal and liposomal formulation of lamivudine was prepared. The entrapment efficiency of ethosomes was found to be $57.2\% \pm 2.5\%$ due to the presence of ethanol in vesicular membrane as compared to liposomes which showed less entrapment efficiency of $41.4\% \pm 1.7\%$ only. It was suggested that with increase in concentration of ethanol from 15 to 45%, the entrapment efficiency also increases. However, on further increasing the concentration of ethanol, that is, greater than 45% the vesicle membrane becomes leaky leading to decrease in entrapment efficiency. Skin permeation test studied on rats using franz diffusion cell. Transdermal flux of ethosome formulation increases $68.4 \pm 3.5 \mu\text{g}/\text{cm}^2/\text{hour}$ with increase in ethanol concentration upto 45%. Also ethosomes flux was 8-fold higher, 12-fold higher, 15-fold higher, 5 and 25-fold higher than that of 2% phospholipid solution in ethanol, ethanolic solution of drug, hydroalcoholic solution of drug, liposomal and drug solution in phosphate buffer saline, respectively. The cytotoxicity assay concluded that cytotoxic effect of lamivudine can be decreased by encapsulating the drug in the vesicular formulation.^[74]

Class-II Non-nucleoside-based Reverse Transcriptase Inhibitors

The non-nucleoside reverse transcriptase inhibitors (NNRTIs) are a structurally and chemically dissimilar group of antiretroviral that are highly active against HIV-1 reverse transcriptase. These are not active against other retroviral reverse transcriptase enzymes, such as HIV-2, hepatitis

viruses, herpes viruses, and mammalian enzyme systems, are unaffected by these compounds.^[75] These compounds induce a conformational change in the three-dimensional structure of the enzyme thereby reducing its activity, and thus they act as noncompetitive inhibitors. They are active in their native state, requiring no phosphorylation or other activity-dependent alteration.

Nevirapine

Nevirapine was the first NNRTI to be licensed. It is a dipyridodiazepinone NNRTI with potent activity against HIV-1.

Liposomal nano delivery system for nevirapine was developed by Ramana *et al.* In this study liposomes were prepared from egg phospholipids using film hydration. By using different ratios of egg phospholipid to cholesterol, and drug to total lipid, the encapsulation efficiency of liposomes was optimized. The results demonstrated that the encapsulation efficiency of egg phospholipid to cholesterol ratio of 9:1 was found to be 78.14 % and that of drug to lipid ratio of 1:5 was found to be 76.25 %. The drug release from liposome was performed in different experimental conditions, that is, in phosphate buffer saline, Dulbecco's Modified Eagle's Medium (DMEM) supplemented with 10 % fetal bovine serum or in the presence of an external stimulus such as low-frequency ultra sound. It was observed that 40%, 60% and 100% drug was released in first 20 minutes when placed in PBS, DMEM or when ultrasound was applied, respectively. Hence, nevirapine-loaded liposomal nanodelivery was proved to improve targeted delivery of antiretroviral drug with reduced side effects.^[76]

Efavirenz

Efavirenz is chemically described as (S)-6-chloro-(cyclopropylethynyl)-1,4-dihydro-4-(trifluoromethyl)-2H-3,1-benzoxazin-2-one. Efavirenz (EFV; Sustiva®) is a highly lipophilic NNRTI. It is classified in class II of the biopharmaceutic classification system.^[77]

A recent article of efavirenz explained successful reduction in dose of efavirenz which was guided by therapeutic drug monitoring.^[78] Correct dose reduction can be calculated by the use of a standardized Bayesian algorithm. This dose reduction enabled to target therapeutic range (1,000-4,000 ng/ml), without reaching the subtherapeutic concentrations.

Class-III PIs

In HIV and many other viral infections, the mRNA transcribed from the provirus is translated into two biochemically inert *polyproteins*, which is further converted by a virus-specific protease into various structural and functional proteins by cleavage at the appropriate positions. This protease does not occur in the host, and considered to be a useful target for chemotherapeutic intervention.

HIV-specific PIs bind to the site where cleavage occurs, and their use, in combination with reverse transcriptase inhibitors, has transformed the therapy of AIDS.^[79]

Ritonavir

It is a potent PI and CYP3A4 inhibitor. Ritonavir-boosted PIs are one of the first-line regimens recommended for treatment-naive patients and play a primary role in second-line regimens and therapy for treatment-experienced patients. The six PIs recommended for the treatment of HIV infection are lopinavir, atazanavir, fosamprenavir, darunavir, tipranavir, and saquinavir. Except atazanavir, all are in combination with ritonavir boosting. Atazanavir is the only PI which may be used without ritonavir-boosting. The low-dose ritonavir used as a pharmacokinetic enhancer, extended the dosing intervals of the primary PI (once or twice daily dosing), with associated improvements in pill burden and adherence, and potency can also be increased with reduced occurrence of resistance as compared to unboosted PIs.^[80]

Ritonavir is classified under class II of biopharmaceutical classification system. The class II corresponds to low solubility and high permeability. One of the approaches used to increase the solubility of poorly soluble drugs is to make solid dispersions. The development of solid dispersions is a novel approach to enhance bioavailability of poorly water-soluble drugs. It also overcame the limitations of previous approaches such as salt formation, solubilization by cosolvents, and particle size reduction which were earlier used to enhance solubility. Ritonavir solid dispersion was prepared using gelucire and sorbitol as carrier in a ratio of 1:4 which were optimized by a phase solubility studies. Both solid dispersions of ritonavir-gelucire and ritonavir-sorbitol were prepared solvent method and melt method. By *in vitro* release profile it was observed that release profile was dependent on the method of preparation of solid dispersion. The solid dispersion prepared by solvent method using gelucire as a carrier showed the maximum release of 85.43% as compared to that with sorbitol as a carrier in which the release was only 45.5%. On the other hand, when melt method was used for preparation using a carrier, gelucire, the release was found to be less i.e., 80.9% only while in the case of sorbitol, the release increased from 45 to 60.9%. The *in vivo* studies were performed in albino Wistar rats revealed that the peak plasma concentration (C_{max}) of ritonavir (containing gelucire as carrier) in Melt method, Solvent method, and pure drug were 2,462.2 + 36.51; 20,221.37 + 35.72; 1,354.8 + 39.47 ng/ml, respectively; while AUC_{0-t} and $AUC_{0-\infty}$ were found to be 5,379.286, 12,649.9, 2,064.44 ngh/ml and 5,403.56, 12,688.12, 2,071.96 ngh/ml, respectively. These values indicated maximum plasma concentration and area under the curve was achieved by solid dispersion formulation prepared by solvent evaporation.^[81]

Saquinavir

Saquinavir is a peptidomimetic hydroxyethylamine HIV PI. Saquinavir inhibits both HIV-1 and HIV-2 replication and has an *in vitro* IC_{50} in peripheral blood lymphocytes that ranges from 3.5 to 10 nM. Cationic submicron emulsions of saquinavir was prepared by standard procedures and characterized its globule size, zeta potential, entrapment efficiency, release profile, cytotoxicity and stability studies. Different charge inducers used in this formulation were chitosan, stearylamine and protamine. The results indicated that the sustained release action was found to be more prominent in case of chitosan emulsion followed by stearylamine emulsion, protamine emulsion, and plain emulsion. The total amount of drug released in 24 hour were 46%, 52%, 56% and 62% associated with chitosan emulsion, stearylamine emulsion, protamine emulsion and plain emulsion, respectively. The permeation flux of saquinavir while using charge inducer chitosan (1 μ g/min) was twice more than plain emulsion. So, it was concluded that using positive charge inducer increase the absorption of drug through intestinal mucosa.^[82]

Nonselective Antiviral Drugs

This group comprises of ribavirin, lamivudine, adefovirdipivoxil, interferon alpha.

Interferon is an active protein used in the treatment of genital warts and herpes infection. A dose comparison study of topical interferon alpha 2b eye drop was done by Galor *et al.* for treatment of ocular surface squamous neoplasia.^[83] In this experiment IFNalpha2b eyedrops 1 million international units/ml was compared with 3 million international units/ml by testing on patients with conjunctival intraepithelial neoplasia and squamous cell carcinoma. Twenty nine and twelve eyes were treated using 1million IU/ml and 3 million IU/ml topical interferon respectively. Moreover, two patients with squamous cell carcinoma, of whom one was treated with 1 million IU/ml another was treated with 3 million IU/ml. The results showed no significant differences between one and three million IU/ml of topical interferon.

CONCLUSIONS

The intent of the paper is to highlight the potential of novel drug delivery techniques as a vital technique in administering the antiviral and antiretroviral agents. The novel advanced delivery systems offer more protective and effective means of the therapy over conventional multidose therapy. Much research effort in developing novel drug delivery system has been focused on controlled release and sustained release dosage forms. Now considerable efforts are being made to deliver the drug in such a manner so as to get optimum benefits. In conclusion, various novel approaches made give a better chance to deliver a therapeutic substance to the target site in drug delivery system, to improve permeability, decrease dosage frequency and enhances bioavailability.

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