Journal for Research in Applied Sciences and Biotechnology

www.jrasb.com

ISSN: 2583-4053

Volume-4 Issue-1 || February 2025 || PP. 27-37

https://doi.org/10.55544/jrasb.4.1.3

Acyclovir Cream: A Compressive Review of Development, Characterization and Therapeutic Efficacy

Dheeraj Kumar[1], Vandana Sahani[2] and Shivanand Patil[3]

[1]Research Scholar, Department of Pharmacy, Shree Dev Bhoomi Institute of Education Science and Technology (SDBIT), Dehradun, INDIA.

[2]Associate Professor, Department of Pharmacy, Shree Dev Bhoomi Institute of Education Science and Technology (SDBIT), Dehradun, INDIA.

[3]Professor, Department of Pharmacy, Shree Dev Bhoomi Institute of Education Science and Technology (SDBIT), Dehradun, INDIA.

[1]Corresponding Author: dk622460@gmail.com

www.jrasb.com || Vol. 4 No. 1 (2025): February Issue

Received: 01-01-2025	**Revised:** 08-01-2025	**Accepted:** 13-01-2025

ABSTRACT

Acyclovir cream is a widely utilized topical antiviral agent for the treatment of herpes simplex virus (HSV) infections, including cold sores and genital herpes. This review aims to provide a comprehensive analysis of the development, formulation, characterization, and therapeutic efficacy of acyclovir cream. The evolution of acyclovir formulations, from oral to topical applications, is discussed, highlighting advancements in drug delivery systems to enhance bioavailability and skin penetration. Key factors influencing the pharmacokinetics and pharmacodynamics of acyclovir cream are reviewed, including the role of excipients, the mechanism of action, and the influence of formulation characteristics such as viscosity, pH, and stability. Furthermore, therapeutic outcomes from clinical studies are summarized, demonstrating the efficacy of acyclovir cream in reducing lesion size, pain, and healing time in HSV-infected patients. Finally, challenges such as patient adherence, resistance, and the need for further improvements in formulation for enhanced therapeutic effect are addressed. This review aims to provide an in-depth understanding of the current status and future directions for acyclovir cream as a primary treatment for localized HSV infections.

Keywords- Acyclovir antiviral, Acyclovir topical, Herpes simplex virus (HSV), Cold sores.

I. INTRODUCTION

Acyclovir is an agent used to treat infections caused by the herpes simplex virus (HSV). Acyclovir is FDA-approved to treat genital herpes and HSV encephalitis. Non-FDA-approved indications are mucocutaneous HSV, herpes zoster (shingles), and varicella zoster (chickenpox). Acyclovir is the first-line treatment for HSV encephalitis. Currently, no other medications are indicated for treating this condition. It is in the antivirals class of drugs. This activity describes the indications, action, and contraindications for acyclovir as a valuable medication in treating HSV infections. This activity will highlight the mechanism of action, adverse event profile, and other key factors (eg, off-label uses, dosing, pharmacodynamics, pharmacokinetics, monitoring, and clinically relevant drug interactions) pertinent to members of the interprofessional healthcare team in the management of HSV infections. Perioral herpes simplex infections are frequently recurrent. According to studies conducted in North America, at least 20% of young adults experience them [1]. The impact these savings have on individual patients is even more socially significant than their remarkable national scale. Many people, especially some of the most vulnerable patients in the population, such as elderly patients with restricted or fixed incomes, may find the cost of some brand-name prescriptions to be prohibitive. On the other hand, patients have more

ISSN: 2583-4053

Volume-4 Issue-1 || February 2025 || PP. 27-37

https://doi.org/10.55544/jrasb.4.1.3

access to generic drug items due to their affordability [2]. Nevertheless, while reducing the length of viral shedding in men, a different study with topical acyclovir (given six times a day) revealed no therapeutic benefit [3]. At the moment, the cosmetic Since there are numerous nanotechnological items in the works, nanotechnology currently controls a large portion of the cosmetics market. The polymer approach is used to construct the systems, which include both natural and manufactured macromolecules. Bangham rediscovered the phospholipid vesicles as "liposomes" in 1965, and they entered the cosmetics sector in 1986 [4]. The microemulsion A thermodynamically stable transparent, single optically isotropic liquid system consisting of water, oil, and surfactants—often in conjunction with appropriate cosurfactants—is referred to as a microemulsion [5, 6].

The lipids are utilized to create solid lipid nanoparticles, which the body can tolerate. Fatty acids, which make up glycerides, are found in the parenteral feeding emulsion. Because SLNs may be manufactured using straightforward processes like high-pressure homogenization, their large-scale production is simple. As an alternative, the microemulsion process can also be used to prepare SLN [7].

Additionally, Schulman and colleagues coined the word "microemulsion" in 1959 to refer to the clear fluid systems that were produced by titrating an ordinary milky emulsion (macroemulsion) to the point of clarity by adding a medium chain alcohol, such as pentanol or hexanol. According to Schulman, the word "microemulsion" was adopted because of the large droplet size (100-600 nm), which contributed to their transparent appearance. Acyclovir's limited penetration efficacy necessitates increasing treatment frequency, frequently five times per day, which causes discomfort for the patient (Fig. 1).[8].

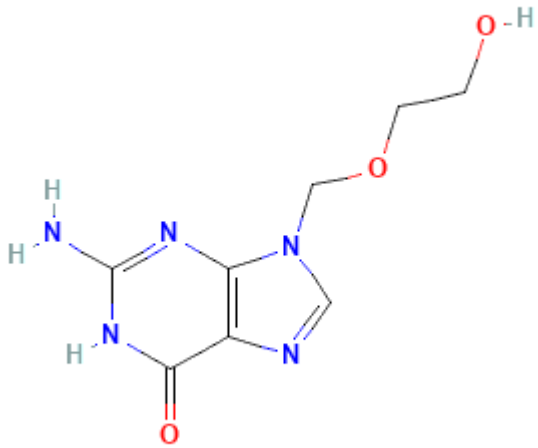

Fig. 1 Structure of acyclovir

Many formulation scientists are motivated to develop improved formulation strategies because to the low penetration effectiveness of the acyclovir topical formulations that are already on the market. Shishu et al., for instance, have improved the topical administration of acyclovir by creating a formulation based on microemulsions. The microemulsion was prepared using isopropyl myristate as an oil, Tween 20, as a surfactant, and Span 20 as a co-surfactant. In comparison to the commercial solution, the adjusted formulation had a greater penetration coefficient and enhanced the fix by 1.7 times [9]. Since drug concentrations in the plasma, serum, or whole blood reflect drug availability at the site of action, in vivo pharmacokinetic investigations are ideal for the majority of medications that act systemically.

We must, however, expand our understanding of in vivo pharmacokinetic research to encompass techniques that measure concentrations at or close to the site of action in order to apply locally active topical dose forms. For instance, pharmacokinetic sampling in microdialysis is carried out by implanting an open-flow microperfusion or dermal microdialysis probe into the dermis and tracking the local drug concentration in the skin over time [9, 10].

Antiviral Agent

The Food and Drug Administration (FDA) in the United States has approved antiviral medicines as medications to treat or manage viral infections. The creation of antiviral drugs is not a simple task since viral replication is so closely related to the host cell that, depending on the dosage and duration of use, any antiviral medication that even slightly disrupts host cell components could be harmful to the host.

Viral latency states can occur when viruses remain in cells in an episomal form or integrate into the host's chromosomal DNA without actively replicating. Although the majority of antiviral medications are primarily effective against replicating viruses, the perfect antiviral medication should be able to combat both latent and actively reproducing viruses [12]. Over 170 million people worldwide are afflicted with the Hepatitis C virus (HCV), with 80% of those cases being chronic. This is around half the number of people infected with the Hepatitis B virus (HBV) and four times the number of people infected with HIV [13].

Acyclovir mechanism of action

Acyclovir, an acyclic purine nucleoside analog, has very little damage to healthy host cells and is a very strong inhibitor of varicella zoster virus and herpes simplex virus (HSV) types 1 and 2. This selectivity results from these viruses' capacity to encode a viral thymidine kinase that can phosphorylate acyclovir to a monophosphate; uninfected cells essentially lack this ability. The goal of antiviral chemotherapy is to prevent virus multiplication without endangering the host. In the past, substances that were effective against DNA viruses also had an impact on healthy cells' DNA.

Journal for Research in Applied Sciences and Biotechnology

www.jrasb.com

ISSN: 2583-4053

Volume-4 Issue-1 || February 2025 || PP. 27-37

https://doi.org/10.55544/jrasb.4.1.3

The mechanism of action and selectivity of acyclovir (acyclo-Guo, 9-(2-hydroxyethoxymethyI) guanine) were thoroughly investigated after it was found to be a powerful inhibitor of the reproduction of herpes simplex virus types 1 and 2 (HSV-1, HSV-2) with very little toxicity for the host cells [14]. One special characteristic of acyclovir is that it selectively inhibits the replication of the herpes simplex virus. Compared to cellular DNA pymerase, viral DNA polymerases have an affinity for acyclovir triphosphate that is 10–30 times higher. The triphosphate derivative is used as a substrate by the HSV-I and HSV-2 DNA polymerases. DNA synthesis stops when acyclovir triphosphate is added to the expanding DNA chain [15].

A thorough examination has been conducted into the mechanism of action of acyclovir. It has been discovered that acyclovir's antiviral action on varicella zoster virus and herpes simplex viruses stems from its interference with DNA synthesis, as detailed in the review of Richards et al. (1983).

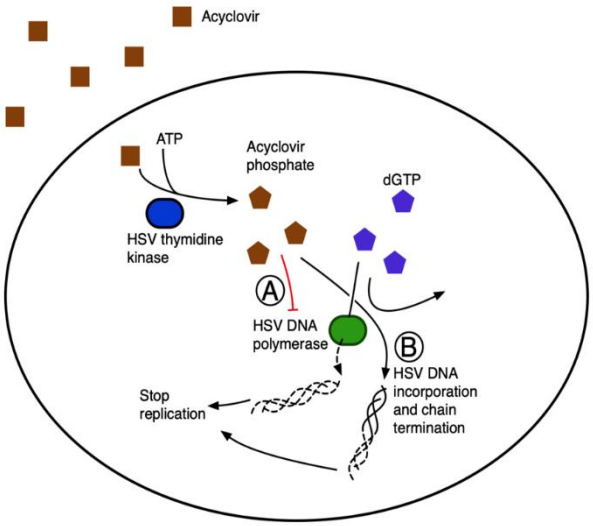

Fig: 2 Mechanism of action of acyclovir

II. PHYSICOCHEMICAL PROPERTIES OF ACYCLOVIR

An analogue of guanosine, acyclovir {2-amino-1,9-dihydro-9-[(2-hydroxyethoxy) methyl]-6H-purin-6-one} (Scheme 1) is an antiviral medication. Its low cytotoxicity and selectivity make it one of the most widely used antiviral medications. It is mostly used to treat varicella-zoster virus (VZV) and herpes simplex virus type 1 (HSV-1) and type 2 (HSV-2).1. [17]

Nearly 300,000 new instances of herpes simplex virus type I (HSV-1) infection are recorded each year in the United States, making it an epidemic. A common side effect of this viral infection is herpes simplex keratitis, which is caused by autoimmunization of the ocular tissues. Tearing, conjunctivitis, and punctate keratitis are among the clinical signs of primary herpetic keratitis. Primary herpes keratitis typically resolves on its own without leaving any scars. On the other hand, HSV-1 may stay dormant in the trigeminal ganglion and occasionally shed, resulting in secondary herpetic keratitis symptoms. Twenty percent of patients with ulcerative keratitis will have underlying stromal involvement, and fifty percent of hosts will develop recurrent disease within a year [18].

One commonly used guanine analog antiviral is acyclovir (ACV). When phosphorylated in infected cells, it takes on its active form and stops the virus from growing (Renjini Joseph and Girish Kumar, 2011, Suzuki et al., 2006). Herpes simplex virus I (cold sores) and herpes simplex virus II (genital herpes) infections are prevented and treated with ACV [19].

The formation of highly soluble and stable pharmacological cocrystals is highly promising, as each drug form has distinct features. Improved safety may also result from the use of medicinal excipients as cocrystal formers.

Herpes simplex virus type 1 (HSV-1), type 2 (HSV-2), and varicellar-zoster virus (VZV) can be inhibited by acyclovir (Fig. 3a), a synthetic purine nucleoside analogue that prevents the drug's replication in PEG ointment and may increase transdermal absorption. A number of methods have been developed to improve medication absorption through the skin. They can often be divided into two categories (Benson, 2005) [20].

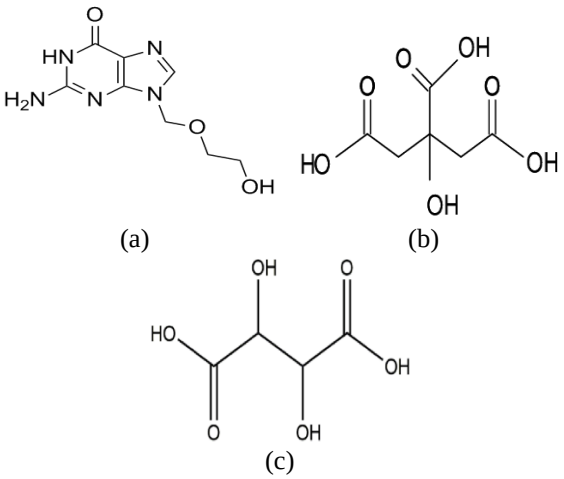

Fig. 3. Chemical structures of acyclovir (a), tartaric acid (b), and citric acid (c).

Pharmacology (Mechanism of action Acyclovir)

From the viewpoint of a clinical pharmacologist, the current state of acyclovir's pharmacokinetic and toxicologic data is examined. A two-compartment open model adequately describes the pharmacokinetics of acyclovir. About two-thirds of the body weight is the volume of distribution in steady state. Its beta phase of elimination has a half-life of roughly three hours when renal function is normal and eighteen

ISSN: 2583-4053

Volume-4 Issue-1 || February 2025 || PP. 27-37

https://doi.org/10.55544/jrasb.4.1.3

hours when anuria is present. About 60% of the acyclovir in the body is eliminated by hemodialysis [21]. It has been demonstrated, using radio labelled acyclovir, that in HSV infected cells, the drug was rapidly metabolised to the mono-, di- and triphosphate whereas these were not detectable in uninfected cells. It was also shown that the HSV-specified thymidine kinase (TK) was responsible for the conversion of acyclovir to its monophosphate [22].

Uses and Administration of Acyclovir cream

Chickenpox, shingles, herpes virus infections of the genitals (sex organs), skin, brain, and mucous membranes (mouth and lips), as well as extensive herpes virus infections in neonates, can all be treated with acyclovir. Acyclovir is also used to stop genital herpes infections from happening again.

Most people have at least one latent infection caused by the varicella zoster virus and the types I and II of the herpes simplex virus. Vesicles and ulcers on the skin, mucous membranes, or both are typically the outcome of both primary and recurring disease. Acyclovir is a strong, targeted antiviral medication that is effective against varicella zoster virus and herpes simplex viruses I and II. It has a very low apparent toxicity. In Britain, it is currently offered as skin cream, oral and intravenous formulations, and ocular ointment. Professor Morag Timbury summed up its mechanism of action and the findings of preliminary clinical trials in a seminal article. The effectiveness of this medication in the prevention and treatment of severe and potentially fatal illnesses has been further supported by research [23].

Precautions and adverse effects

The following medical conditions make acyclovir contraindicated:

Being pregnant: According to Sweet Man (2006), 312 females exposed to acyclovir did not have a higher risk of congenital abnormalities or spontaneous foetus loss than the general population. Manufacturers still only recommend use when the possible advantages outweigh the risks, even though it is not acknowledged to be dangerous (Joint Formulary Committee, 2013).

Breastfeeding: Sweetman (2006) states that acyclovir is transferred to breast milk. Indeed, in certain instances, the measured acyclovir level exceeds the maternal serum level (Andrews et al, 1992). Despite these results, breastfed infants whose moms have taken acyclovir have not experienced any negative side effects (sweetman, 2006). Thus, according to the British National Formulary (Joint Formulary Committee, 2013):[24].

Adverse effects: Because oral acyclovir has a low bioavailability (about 15% of the administered dose) and topical acyclovir is not systemically absorbed, the side effects of both have been minimal. In patients with normal renal function, even the high dosages of oral acyclovir (4 g/day for 10 days) under the current controlled zoster treatment strategy have not been linked to harmful responses [25].

Pharmacokinetics and Bioavailability of the Acyclovir:

In early research, healthy male volunteers were given single doses of acyclovir to evaluate its safety and absorption. The mean percentage of acyclovir dose recovered unchanged in the urine decreased from 13-2 to 6% in one research (Brigden et al., 1980) when doses were increased from 100 to 600 mg. This suggests that acyclovir absorption is dose-dependent following single-dose delivery [26]. Therefore, the bioavailability of the innovator preparation, Zovirax, and a local generic preparation of acyclovir, Avorax, was compared in the current investigation. Furthermore, an effort was undertaken to evaluate the pharmacokinetics of acyclovir in the Asian local population, which has not been studied before [27].

Absorption: Nasal systemic drug delivery is currently gaining a lot of attention due to its many benefits, which include quick absorption and pharmacological effect onset, avoidance of liver first pass metabolism, high systemic availability, and an easy administration route that is especially well-suited for self-medication. Orally taken ACV has a bioavailability of around 15–30% and is absorbed slowly, inconsistently, and incompletely. ACV is mostly transported across the buccal region by a passive diffusion process, most likely via the paracellular pathway, according to an in vitro research conducted on swine buccal tissue. As a result, this substance might be a useful model medication for research on nasal absorption enhancement using absorption enhancers [28].

III. DISTRIBUTION

In immunocompetent subjects, the limited effectiveness of dermatological formulations of ACV for recurring infections was ascribed to both variable drug distributions in skin layers and insufficient drug percutaneous penetration. Compared to ACV made in polyethylene glycol, better antiviral outcomes have been obtained with a modified aqueous cream or a barrier-altering solvent (dimethylsulfoxide) [29].

Infectious virus distribution in CD-1 mice following intraperitoneal HSV-2 infection, with or without ACV therapy. As previously mentioned, ACV (80 mg/kg daily) was administered to infected CD-1 mice. By extracting organs at the designated dates and measuring the infectious virus levels on Vero cells using a plaque assay, the infection's progression was tracked. According to an in vitro plaque reduction assay, the virus recovered from the kidneys and brains of mice treated with ACV on days 4 and 6, respectively, was equally sensitive to ACV as the initial virus population [30].

Metabolism

8-hydroxy-9-(2-hydroxyethoxymethyl) guanine is regarded as the minor metabolite of acyclovir, while 9-carboxymethoxymethylguanine (CMMG) is the predominate and pharmacologically inactive19

ISSN: 2583-4053

Volume-4 Issue-1 || February 2025 || PP. 27-37

https://doi.org/10.55544/jrasb.4.1.3

metabolite. The kidney is actively involved in drug metabolism in addition to its well-defined physiological roles, which include osmolarity regulation, electrolyte balance maintenance, hormone synthesis, and waste material elimination. [31]

In both virus-infected and uninfected cells, the metabolism of acyclovir to its mono-, di-, and triphosphate derivatives was investigated. Acyclovir phosphorylation was influenced by the kind of virus, cell line, concentration of the exogenous medication, and duration of exposure. Exogenously administered nucleosides hindered the phosphorylation of acyclovir. [32].

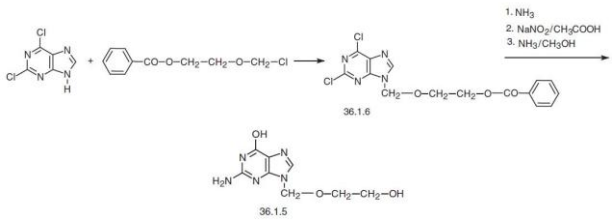

Fig. 4 Synthesis of metabolism acyclovir

Elimination

Strong anti-herpesvirus medication acyclovir is primarily excreted by the kidneys. Less than 14% of the supplied dose is made up of 9 carboxy methoxymethyl guanine, the only major acyclovir metabolite that has been identified to far. To clarify the function of organic acid transport in the destiny of different medications, probenecid, an inhibitor of the organic acid transport system, has been widely used [33]. Topical formulations are generally much safer and more effective than systemic administration [34].

Drug interaction of acyclovir

After oral administration, hepatic first-pass metabolism largely transforms valaciclovir (Valtrex), the L-valine ester of acyclovir, into the antiherpetic drug acyclovir. The oral bioavailability of valaciclovir is three to five times higher than that of acyclovir [35].

Product and development

In 2002, the US Food and Drug Administration authorized Zovirax cream for the treatment of recurring cold sores, or herpes labialis, in adults and adolescents. Inactive ingredients include cetostearyl alcohol, mineral oil, poloxamer 407, propylene glycol, sodium lauryl sulfate, water, and white petrolatum. The product is a topical dermatological treatment that contains 5% w/w of acyclovir in an aqueous cream base (Zovirax, 2002) [36].

Acyclovir antiviral pharmacology

These include idox-uridine, trifluorothymidine, and adenine arabinoside (ara-A) for ocular herpes, ara-A for herpes encephalitis and disseminated zoster in immunocompromised patients, mar-boran (N-methylisatin-B-thiosemicarbazone) for smallpox vaccination complications, and amanta-dine hydrochloride for influenza A infection prevention and treatment in high-risk groups [37]. medicine development in the US and the Food and Drug Administration's (FDA) final clearance of a medicine for clinical use involve a number of procedures to show that the drug works for the intended use and can be taken with a manageable level of toxicity.

The average duration between a new chemical entity's synthesis and FDA approval for compounds approved in the 1980s and early 1990s was 13 to 15 years [38]. A number of enzymes that are incompatible with cellular enzymes are encoded by herpesviruses. These include ribonucleotide reductase, DNA polymerase, and thymidine kinase (reviewed in Kit, 1979). Early research by Elion et al. (1977) showed that (1) the viral thymidine kinase selectively phosphorylates acyclovir, (2) acyclovir triphosphate effectively inhibits the HSV-I DNA polymerase's ability to compete with dGTP, and (3) acyclovir monophosphate is integrated into DNA, which stops DNA synthesis [39].

Safety and Tolerability

The VAS, lesional score, pruritus, and the emergence of new lesions were the effectiveness criteria. Patients used a VAS of 1–10 to measure the decrease in itching [40]. Vital signs, treatment-emergent clinical adverse events, and standard hematological and biochemical assays were also included of the safety evaluation [41]. Herpes simplex virus (HSV), mainly HSV type 1 (HSV-1), is the cause of herpes simplex labialis (HSL), commonly referred to as cold sores or feverblisters. In immunocompetent people, recurrent HSL lesions typically persist 10 days and are most common on the lips. Prodrome with itching and stinging, erythema (macule), papule, vesicle, ulcer or soft crust, hard crust, residual abnormalities (dry flaking skin and residual swelling and erythema), and re-epithelialization and healing (normal skin) are the distinct stages that classical HSL recurrences go through.

The longest and most important phases for the person are the vesicle and ulcer or soft-crust stages [42]. Due to a lack of IV acyclovir in late 2011, patients with confirmed herpes simplex virus (HSV) meningitis or encephalitis had to experimentally switch to high-dose oral valacyclovir (HDVA) in order to save IV acyclovir. This study details the usage of HDVA and the Antimicrobial Stewardship Program (ASP) at Northwestern Memorial Hospital (NMH), Chicago, IL, USA, in managing the most recent nationwide IV acyclovir shortage. Second, during this scarcity, we evaluated HDVA's safety and tolerability as a substitute for IV acyclovir [43].

Herpes zoster is more prevalent in people who have had chemotherapy, radiation therapy, or underlying diseases that have severely impaired their immune systems than in the general population. Patients with Hodgkin's disease and non-Hodgkin's lymphoma are most likely to experience it. Due to the development of visceral dispersion, varicella-zoster virus (VZV) infections can progress to a very dangerous stage in

ISSN: 2583-4053

Volume-4 Issue-1 || February 2025 || PP. 27-37

https://doi.org/10.55544/jrasb.4.1.3

immunocompromised individuals [Feldman et al., 1973; Locksley et al., 19851]. Immunocompromised patients also have a higher chance of delayed lesion healing and cutaneous rash progression. Significant advancements have been made in the targeted treatment of VZV infections over the past ten years. In addition to acyclovir [Balfour et al., 19831] and vidarabine [Whitley et al., 1976, 1992], brivudin [Benoit et al., 1985; De Clercq et al., 1980a; It has been demonstrated that in immunocompromised patients, Wildiers and De Clercq, 1984; Tricot et al., 1986; Wutzler et al., 19881 can stop the progression of herpes zoster. Other potential medications for VZV infections that are presently being evaluated include sorivudine (BVaraU) [Boag et al., 19941], penciclovir and its oral prodrug famciclovir [Tyring et al., 19931], and valaciclovir [Purifoy et al., 19931 (the oral prodrug of acyclovir). In order to treat herpes zoster in adult patients with malignant illness, the results of a randomized double-blind experiment comparing oral brivudin and intravenous acyclovir are presented [44].

IV. VARIOUS DRUG DELIVERY OF ACYCLOVIR

Because of its ease of administration, patient compliance, formulation flexibility, and other factors, oral delivery is the most preferred method of drug delivery [45]. Only when taken multiple times daily can conventional drug delivery systems attain and sustain the medication concentration within the therapeutically effective range required for treatment. Drug levels fluctuate significantly as a result [46]. Numerous novel drug delivery systems (NDDS) have been developed as a result of various technological breakthroughs, and they have the potential to transform medication delivery and offer numerous therapeutic advantages. The following are the main goals of these NDDS: (a) ideally a single dose throughout the course of treatment. (b) Drug delivery that is site specific, reducing or even eliminating adverse effects [47].

More than one-third of the world's population has been afflicted by the herpes simplex virus (HSV), which is thought to be present in between 30% and 70% of Asian populations overall. HSV causes a wide range of illnesses in humans, from pain to death.[48] Herpes viruses are thought to be present in 60% of sexually active adults in India. Approximately 86 million people worldwide suffer with genital herpes at this time. Among people who are HIV-positive, genital herpes is the most prevalent infection [49].

In actuality, HSV-2 antibodies are present in 60–85% of HIV-positive individuals. HIV is more likely to infect people with genital herpes than people without the infection. HIV and genital herpes (GH) can both be spread through sexual contact.[50]

V. ORAL DELIVERY SYSTEMS:

Acyclovir is an antiviral medication that is frequently used to treat illnesses brought on by the varicella-zoster virus (VZV) and herpes simplex viruses (HSV-1 and HSV-2). Its oral delivery methods are made to minimize dosage frequency, enhance therapeutic results, and maximize bioavailability.

1. Challenges in Oral Delivery of Acyclovir

There are various obstacles to oral administration of acyclovir: **limited Oral Bioavailability:** When taken orally, acyclovir has a bioavailability of just 10–30% due to its limited permeability and poor water solubility. **Frequent Dosing:** Acyclovir needs several daily doses due to its brief plasma half-life (2–3 hours), which compromises patient compliance. Inadequate Solubility: Impacts gastrointestinal absorption.

2. Conventional Oral Delivery of Acyclovir

Immediate-Release Tablets or Capsules

In the stomach, standard formulations dissolve rapidly.

Needs to be taken frequently (200 mg five times a day for HSV, for example).

Liquid Suspensions

Designed for pediatric or geriatric patients.

Provides flexibility in dosing but still suffers from low bioavailability.

3. Modified-Release Systems

Sustained-Release Formulations

Designed for pediatric or geriatric patients.

Provides flexibility in dosing but still suffers from low bioavailability.

Prodrugs (Valacyclovir)

A prodrug of acyclovir, valacyclovir has a much higher oral bioavailability (~55%).

Transformed by enzymatic hydrolysis in the liver into acyclovir.

Less frequent dosing is needed than with acyclovir.

4. Nanotechnology-Based Systems

Nanoparticles

Enhances the GI tract's medication permeability and solubility.

Increases acyclovir's stability and bioavailability.

Liposomes and Solid Lipid Nanoparticles (SLNs)

Prevent the GI tract from breaking down acyclovir. Provide a targeted and regulated release of drugs.

5. Mucoadhesive and Buccal Delivery Systems

1. Mucoadhesive Gels or Tablets 6:

Baccal Patches sustained administration that improves systemic absorption through the buccal mucosa. 7. Oral Acyclovir's Future Directions 8. Cutting Edge Nanocarriers advancements in micelles and nanoparticles based on polymers for sustained and tailored release. Tablets with 3D Printing Customize release profiles and dosages according to patient requirements. Combination therapies are

ISSN: 2583-4053

Volume-4 Issue-1 || February 2025 || PP. 27-37

https://doi.org/10.55544/jrasb.4.1.3

formulations that increase permeability and decrease virus resistance by mixing acyclovir with adjuvants.

2. Topical Delivery Systems:

Topical delivery systems are methods or technologies designed to administer active pharmaceutical ingredients (APIs), therapeutic agents, or cosmetics directly onto the skin or mucosal surfaces to achieve localized or systemic effects. These systems play a crucial role in improving drug efficacy, patient compliance, and targeted delivery. Below is an overview of common types and advancements in topical delivery systems:

3. Parenteral (Injectable) Delivery Systems:

Parenteral delivery systems are methods of administering drugs directly into the body through injections, bypassing the gastrointestinal tract. These systems are critical for drugs that require rapid onset of action, are poorly absorbed orally, or are unstable in the digestive environment. Below is a comprehensive overview.

Type of parenteral drug delivery system

- Intravenous (IV)
- Intramuscular (IM)
- Subcutaneous (SU)
- Intradermal (ID)

4. Inhalation Delivery System

Inhalation delivery systems are designed to deliver drugs directly into the respiratory tract, where they can exert local or systemic effects. These systems are particularly effective for conditions affecting the lungs, such as asthma or chronic obstructive pulmonary disease (COPD), and for delivering drugs with rapid systemic absorption via the pulmonary circulation. Below is a detailed overview of inhalation delivery systems:

Types of Inhalation Delivery Systems

Metered-Dose Inhalers (MDIs)

- Pressurized devices that release a fixed dose of medication in aerosol form.
- Require coordination between actuation and inhalation.
- Often used for bronchodilators and corticosteroids.

Dry Powder Inhalers (DPIs)

- Contain powdered medications activated by the patient's breath.
- Do not require propellants but depend on the user's inspiratory effort.
- Suitable for drugs like long-acting beta-agonists and anticholinergics.

Nebulizers

- Convert liquid medication into a fine mist for inhalation.
- Ideal for patients who cannot use MDIs or DPIs effectively (e.g., children, elderly).
- Commonly used in hospitals for severe respiratory conditions.

Soft Mist Inhalers (SMIs)

- Produce a slow-moving, fine mist for better drug deposition in the lungs.
- Require less coordination than MDIs.

Nasal Inhalers

- Deliver drugs via the nasal passages for localized effects (e.g., nasal decongestants) or systemic effects (e.g., vaccines, peptides).

5. Nano systems:

Nano systems refer to nanoscale technologies and materials engineered for the delivery of drugs, therapeutic agents, or diagnostics. These systems, typically ranging from 1 to 100 nanometers in size, offer enhanced precision, controlled release, and targeted delivery, addressing limitations of conventional therapies. Below is an overview of nano systems in medicine and pharmaceuticals

1. Types of Nano Systems

1.1 Nanoparticles

- **Polymeric Nanoparticles**
  - Biodegradable polymers like PLGA or chitosan encapsulate drugs for sustained release.
  - Ideal for vaccines, cancer therapies, and gene delivery.
- **Solid Lipid Nanoparticles (SLNs)**
  - Lipid-based particles offering controlled release and stability for hydrophobic drugs.
  - Used in cosmetics and pharmaceuticals.

1.2 Liposomes

- Spherical vesicles composed of lipid bilayers.
- Encapsulate hydrophilic drugs in the core and hydrophobic drugs in the bilayer.
- Applications: cancer therapies (e.g., Doxil), antifungals, and vaccines.

1.3 Nanomicelles

- Amphiphilic molecules self-assemble into nanosized carriers.
- Enhance solubility of poorly water-soluble drugs.
- Widely used in chemotherapy.

1.4 Dendrimers

- Branched, tree-like polymers with a well-defined structure.
- Functionalized surfaces for drug conjugation and delivery.
- Applications: targeted drug delivery and gene therapy.

1.5 Quantum Dots

- Semiconductor nanoparticles emitting fluorescence for imaging and diagnostics.
- Applications: cancer diagnostics and bioimaging.

1.6 Carbon-Based Nano Systems

ISSN: 2583-4053
Volume-4 Issue-1 || February 2025 || PP. 27-37
https://doi.org/10.55544/jrasb.4.1.3

- **Carbon Nanotubes:** Cylindrical carbon molecules used for drug and gene delivery.
- **Graphene Oxide:** Utilized for drug delivery, imaging, and photothermal therapy.

6. Mucosal Delivery Systems:

Mucosal delivery systems are designed to administer drugs through the body's mucosal surfaces, including the oral, nasal, pulmonary, rectal, vaginal, and ocular regions. These systems leverage the high vascularization and permeability of mucosal tissues, offering rapid absorption, localized effects, and in some cases, systemic delivery.

Types of Mucosal Delivery Systems

3.1 Films and Patches

- Thin, flexible systems adhere to mucosal surfaces for controlled drug release.
- Examples: Buccal films for opioids, vaginal patches for contraceptives.

3.2 Gels and Ointments

- Semi-solid systems provide localized treatment and longer retention.
- Examples: Nasal gels for congestion, ocular ointments for infections.

3.3 Microparticles and Nanoparticles

- Enhance drug stability, penetration, and sustained release.
- Examples: Nanoparticles for nasal vaccines or rectal anti-inflammatory agents.

3.4 Sprays and Aerosols

- Deliver drugs in fine particles for nasal or pulmonary absorption.
- Examples: Nasal sprays for hormonal therapies or pulmonary inhalers for insulin.

3.5 Suppositories and Rings

- Used for rectal and vaginal delivery of drugs.
- Examples: Vaginal rings for contraception, rectal suppositories for fever.

3.6 Hydrogels and Mucoadhesive Systems

- Provide prolonged residence time on mucosal surfaces, improving drug absorption.
- Examples: Mucoadhesive patches for oral ulcers or hydrogels for wound care.

7. Ocular (Eye) Delivery Systems:

Ocular delivery systems are specialized drug delivery methods designed to treat eye diseases or conditions. These systems address the unique challenges posed by the eye's anatomy and physiological barriers, ensuring localized or systemic drug delivery with minimal side effects.

Types of Ocular Delivery Systems

2.1 Topical Systems

- **Eye Drops**
  - Most common form, targeting the anterior segment.
  - Examples: Lubricants, antibiotics, anti-inflammatory agents.
- **Gels and Ointments**
  - Increase drug residence time on the eye surface.
  - Examples: Artificial tear gels, antibiotic ointments.

2.2 Intraocular Injections

- **Intravitreal Injections**
  - Deliver drugs directly into the vitreous humor for posterior segment diseases.
  - Examples: Anti-VEGF agents for macular degeneration.
- **Subconjunctival Injections**
  - Administered beneath the conjunctiva for prolonged drug release.

2.3 Implants

- **Biodegradable Implants**
  - Slowly degrade, releasing drugs over weeks or months.
  - Examples: Dexamethasone implants for uveitis.
- **Non-Biodegradable Implants**
  - Require surgical removal after drug release.
  - Examples: Retisert for chronic posterior uveitis.

2.4 Contact Lens-Based Systems

- Drug-loaded contact lenses for sustained release to the cornea.
- Applications: Glaucoma and dry eye treatments.

2.5 Nano and Microparticle Systems

- **Nanoparticles**: Enhance penetration into ocular tissues.
- **Liposomes and Micelles**: Improve drug solubility and stability.
- Applications: Delivery of hydrophobic drugs or gene therapy agents.

2.6 Hydrogels and Mucoadhesive Systems

- Retain drugs on the ocular surface for prolonged effect.
- Examples: Hydrogels for dry eye treatment.

2.7 Iontophoresis

- Non-invasive technique using electrical current to enhance drug penetration.
- Applications: Delivery of antibiotics or anti-inflammatory agents.

2.8 Ocular Inserts

- Thin films placed in the conjunctival sac for controlled drug release.
- Examples: Pilocarpine inserts for glaucoma.

8. Implants or Intra-Articular Injections:

Implants and intra-articular (IA) injections are drug delivery systems designed to provide localized, controlled, and sustained drug release for specific conditions, particularly in orthopedic and chronic pain management. These approaches are especially beneficial for targeting joints or tissues where systemic treatments are less effective.

ISSN: 2583-4053
Volume-4 Issue-1 || February 2025 || PP. 27-37
https://doi.org/10.55544/jrasb.4.1.3

Types of Implants

a) Biodegradable Implants

- Made from polymers like PLGA or PCL, which degrade over time, eliminating the need for removal.
- Examples: Zoladex (goserelin implant for cancer and endometriosis).

b) Non-Biodegradable Implants

- Require surgical removal after drug depletion.
- Examples: Retisert (fluocinolone acetonide implant for uveitis).

c) Reservoir-Based Implants

- Contain a drug reservoir surrounded by a rate-controlling membrane.
- Applications: Hormonal therapies, ocular diseases.

d) Matrix-Based Implants

- Drug dispersed within a polymeric matrix for diffusion-controlled release.
- Applications: Bone regeneration and anti-inflammatory treatments.

VI. CONCLUSION

Acyclovir remains the gold standard in the treatment of herpes virus infections, mainly due to the emerging of the new delivery systems improving considerably its bioavailability. The analogues of acyclovir, especially their esters, characterized by significantly higher bioavailability and safety, may gradually replace acyclovir in selected applications. Generation of nanocrystals of medium soluble drug is challenging due to possibility of supersaturation and recrystallization. However, physically and chemically stable nanocrystals of medium soluble drug acyclovir were generated using optimal formulation and production technique. The nanocrystals exhibited higher saturation solubility and dissolution rate in comparison to coarse acyclovir, which improved passive diffusion of drug through different layers of the skin by increased concentration

REFERENCES

[1] Ship II, Brightman VJ, Laster LL. The patient with recurrent aphthous ulcers and the patient with recurrent herpes labialis; a study of 2 population samples. Y Am Dent Assoc 1967; 75:645.

[2] Kesselheim AS, Huybrechts KF, Choudhry NK, Fulchino LA, Isaman DL, Kowal MK, et al. Prescription drug insurance coverage and patient health outcomes: a systematic review. Am J Public Health. 2015;105:e17–30

[3] Reichman RC, Badger GJ, Guinan ME, Nahmias Al, Keeney RE, Davis LG, Ashigkaga T, Dolin R. Topically administered acyclovir in the treatment of recurrent herpes simplex infection: a controlled trial. 1 Infect Dis 1983;147:336-40

[4] Müeller H, Maeder K, Gohla S. Solid lipid nanoparticles (SLN) for controlled drug delivery - A review of the state of the art. Eur J Pharmaceut Biopharmaceut 2000; 50: 161-77.

[5] Kumar, R., Saha, P., Kumar, Y., Sahana, S., Dubey, A., & Prakash, O. (2020). A review on diabetes mellitus: type1 & Type2. *World Journal of Pharmacy and Pharmaceutical Sciences*, *9*(10), 838-850.

[6] Kumar, R., Saha, P., Lokare, P., Datta, K., Selvakumar, P., & Chourasia, A. (2022). A systemic review of Ocimum sanctum (Tulsi): Morphological characteristics, phytoconstituents and therapeutic applications. *International Journal for Research in Applied Sciences and Biotechnology*, *9*(2), 221-226.

[7] Kumar, R., & Saha, P. (2022). A review on artificial intelligence and machine learning to improve cancer management and drug discovery. *International Journal for Research in Applied Sciences and Biotechnology*, *9*(3), 149-156.

[8] Bind, A., Das, S., Singh, V. D., Kumar, R., Chourasia, A., & Saha, P. (2020). Natural bioactives for the potential management of gastric ulceration. *Turkish Journal of Physiotherapy and Rehabilitation*, *32*(3), 221-226.

[9] *Johnson M. Transcutaneous Electrical Nerve Stimulation: mechanisms, Clinical Application and Evidence. Rev Pain. 2007;1(1):7–11*

[10] Nyarko, R. O., Awuchi, C. G., Kumar, R., Boateng, E., Kahwa, I., Boateng, P. O., ... & Saha, P. (2022). Effect of Calotropis Procera Extract on Appetitte, Body Weight & Lipid Profile in Cafeteria Diet Induced Obesity in Experimental Animal. *Journal for Research in Applied Sciences and Biotechnology*, *1*(3), 107-113

[11] Dannielsson I, Lindman B. The definition of microemulsion; Colloids and Surfaces 1981; 3: 391-392. Nfluence of microemulsions on cutaneous drug delivery; Advanced Drug Delivery Reviews 2002;54 Suppl. 1: S77–S98. N for topical administration of ydro-micelle. Nature 1943; 152: ulsions by electron microscopy, J. al Permeation of Hydrocortisone f Aceclofenac. AAPS delivery of aspirin; water, propylene glycol,

[12] El-laithy HM, El-shoboury KMF. The developmental cutina lipogel and gel microemulsion fluconazole. AAPS. Pharm. Sci. Tech 2002;3 (4) 35: 1-9

ISSN: 2583-4053

Volume-4 Issue-1 || February 2025 || PP. 27-37

https://doi.org/10.55544/jrasb.4.1.3

[13] Mehnert W, Mäder M. Solid lipid nanoparticles: Production, characterization and applications. Advanced Drug Del Rev 2001; 47: 165–96.

[14] Schulman JH, Stoeckenius W, Prince LM. Mechanism of formation and structure of micro emulations by electron microscopy, J. Phys. Chem. 63 (1959) 1677–1680.

[15] Shishu SR. Development of novel microemulsion-based topical formulations of acyclovir for the treatment of cutaneous herpetic infections. AAPS Pharm SciTech. 2009; 10:559.

[16] Chaurasia C, Muller M, Bashaw E, Benfeldt E, Bolinder J, Bullock R, et al. AAPS-FDA workshop white paper: microdialysis principles, application and regulatory perspectives. Pharm Res. 2007;24:1014–25.

[17] Holmgaard R, Nielsen JB, Benfeldt E. Microdialysis sampling for investigations of bioavailability and bioequivalence of topically administered drugs: current state and future perspectives. Skin Pharmacol Physiol. 2010;23:225–43.

[18] Antiviral Agents. wwwsciencedirectcom [Internet]. 2019 Jan 1 [cited 2021 Jul 2];176–225. Available from: https://www.sciencedirect.com/science/article/pii/B9780128012383023874

[19] Bryan-Marrugo OL, Ramos-Jiménez J, Barrera-Saldaña H, Rojas-Martínez A, Vidaltamayo R, Rivas-Estilla AM. History and progress of antiviral drugs: From acyclovir to direct-acting antiviral agents (DAAs) for Hepatitis C. Medicina Universitaria [Internet]. 2015 Jul 1;17(68):165–74. Available from: https://www.elsevier.es/es-revista-medicina-universitaria-304-articulo-history-progress-antiviral-drugs-from-S166557961500037X

[20] Elion GB. Mechanism of action and selectivity of acyclovir. The American Journal of Medicine. 1982 Jul;73(1):7–13.

[21] Gnann JW, Barton NH, Whitley RJ. Acyclovir: mechanism of action, pharmacokinetics, safety and clinical applications. Pharmacotherapy [Internet]. 1983;3(5):275–83. Available from: https://www.ncbi.nlm.nih.gov/pubmed/635908

[22] O'Brien JJ, Campoli-Richards DM. Acyclovir. Drugs. 1989 Mar;37(3):233–309.

[23] Bruni G, Maietta M, Maggi L, Mustarelli P, Ferrara C, Berbenni V, et al. Preparation and Physicochemical Characterization of Acyclovir Cocrystals with Improved Dissolution Properties. Journal of Pharmaceutical Sciences [Internet]. 2013 Nov [cited 2019 Aug 26];102(11):4079–86. Available from: https://onlinelibrary.wiley.com/doi/full/10.1002/jps.23721

[24] HUGHES PM, KRISHNAMOORTHY R, MITRA AK. Effect of Acylation on the Ocular Disposition of Acyclovir I: Synthesis, Physicochemical Properties, and Antiviral Activity of 2′-Esters. Journal of Ocular Pharmacology and Therapeutics. 1993 Jan;9(4):287–97

[25] Inoue Y, Furuya K, Miruto Matumoto, Murata I, Kimura M, Ikuo Kanamoto. A comparison of the physicochemical properties and a sensory test of Acyclovir creams. International journal of pharmaceutics. 2012 Oct 1;436(1-2):265–71.

[26] Masuda T, Yasuo Yoshihashi, Etsuo Yonemochi, Fujii K, Hidehiro Uekusa, Terada K. Cocrystallization and amorphization induced by drug–excipient interaction improves the physical properties of acyclovir. International Journal of Pharmaceutics. 2012 Jan 17;422(1-2):160–9.

[27] Lietman PS. Acyclovir clinical pharmacology. An overview. The American journal of medicine [Internet]. 1982 [cited 2019 Sep 18];73(1A):193–6. Available from: https://www.ncbi.nlm.nih.gov/pubmed/7048912

[28] Brigden D, Whiteman P. The mechanism of action, pharmacokinetics and toxicity of acyclovir — A review. Journal of Infection [Internet]. 1983 May [cited 2019 Dec 23];6:3–9. Available from: https://www.sciencedirect.com/science/article/abs/pii/S0163445383940410

[29] MEDICAL JOURNAL [Internet]. [cited 2024 Dec 27]. Available from: https://pmc.ncbi.nlm.nih.gov/articles/instance/1417918/pdf/bmjcred00430-0003.pdf

[30] Fromage G. Acyclovir in aesthetic practice: mechanisms of action, medical uses and precautions. Journal of Aesthetic Nursing. 2013 Sep;2(7):338–40.

[31] Balfour HH. Acyclovir Therapy for Herpes Zoster: Advantages and Adverse Effects. JAMA: The Journal of the American Medical Association. 1986 Jan 17;255(3):387.

[32] de Miranda P, Blum MR. Pharmacokinetics of acyclovir after intravenous and oral administration. Journal of Antimicrobial Chemotherapy [Internet]. 1983 Jan 1;12(suppl B):29–37. Available from: https://academic.oup.com/jac/article-abstract/12/suppl_B/29/718421

[33] Yuen KH, Peh KK, Billa N, Chan KL, Toh WT. Bioavailability and Pharmacokinetics of Acyclovir Tablet Preparation. Drug Development and Industrial Pharmacy. 1998 Jan;24(2):193–6.

[34] Chavanpatil MD, Vavia PR. The influence of absorption enhancers on nasal absorption of

ISSN: 2583-4053

Volume-4 Issue-1 || February 2025 || PP. 27-37

https://doi.org/10.55544/jrasb.4.1.3

acyclovir. European Journal of Pharmaceutics and Biopharmaceutics. 2004 May;57(3):483–7

[35] Volpato N. In vitro acyclovir distribution in human skin layers after transdermal iontophoresis. Journal of Controlled Release. 1998 Jan 2;50(1-3):291–6.

[36] Biron KK, Noblin JE, Miranda P de, Elion GB. Uptake, distribution, and anabolism of acyclovir in herpes simplex virus-infected mice. Antimicrobial Agents and Chemotherapy. 1982 Jan 1;21(1):44–50.

[37] Gunness P, Aleksa K, Bend J, Koren G. Acyclovir-induced nephrotoxicity: the role of the acyclovir aldehyde metabolite. Translational Research [Internet]. 2011 Nov 1;158(5):290–301. Available from: https://www.sciencedirect.com/science/article/pii/S1931524411002325

[38] Furman PA, de Miranda P, St Clair MH, Elion GB. Metabolism of acyclovir in virus-infected and uninfected cells. Antimicrobial Agents and Chemotherapy. 1981 Oct 1;20(4):518–24.

[39] Laskin OL, de Miranda P, King DH, Page DA, Longstreth JA, Rocco L, et al. Effects of probenecid on the pharmacokinetics and elimination of acyclovir in humans. Antimicrobial Agents and Chemotherapy. 1982 May 1;21(5):804–7.

[40] Jacob S, Nair AB, Al-Dhubiab BE. Preparation and evaluation of niosome gel containing acyclovir for enhanced dermal deposition. Journal of Liposome Research [Internet]. 2017 Dec 1 [cited 2022 Nov 8];27(4):283–92. Available from: https://pubmed.ncbi.nlm.nih.gov/27558522/

[41] F. De Bony, Tod M, R. Bidault, On N, Posner JB, Rolan P. Multiple Interactions of Cimetidine and Probenecid with Valaciclovir and Its Metabolite Acyclovir. 2002 Feb 1;46(2):458–63.

[42] Yellela S.R. Krishnaiah, Xiao Ming Xu, Rahman Z, Yang Y, Katragadda U, Lionberger R, et al. Development of performance matrix for generic product equivalence of acyclovir topical creams. 2014 Nov 1;475(1-2):110–22.

[43] King DH. History, pharmacokinetics, and pharmacology of acyclovir. Journal of the American Academy of Dermatology [Internet]. 1988 Jan;18(1):176–9. Available from: https://www.sciencedirect.com/science/article/abs/pii/S0190962288700022

[44] Fletcher CV. Pharmacologic Considerations for Antiviral Drug Development. Annals of Pharmacotherapy. 1996 Sep;30(9):972–7.

[45] Reardon JE, Spector T. Acyclovir: Mechanism of Antiviral Action and Potentiation by Ribonucleotide Reductase Inhibitors. Advances in Pharmacology. 1991;1–27.

[46] Reich A, Heisig M, Phan NQ, Taneda K, Takamori K, Takeuchi S, et al. Visual analogue scale: Evaluation of the instrument for the assessment of pruritus. Acta Derm Venereol 2012;92:497-501.

[47] Ehsani A, Esmaily N, Noormohammadpour P, Toosi S, Hosseinpour A, Hosseini M, et al. The comparison between the efficacy of high dose acyclovir and erythromycin on the period and signs of pitiriasis rosea. Indian J Dermatol 2010; 55:246-8.

[48] Strand A, Böttiger D, Gever LN, Wheeler W. Safety and Tolerability of Combination Acyclovir 5% and Hydrocortisone 1% Cream in Adolescents with Recurrent Herpes Simplex Labialis. Pediatric Dermatology. 2011 Oct 17;29(1):105–10.

[49] Caulder CR, Mehta B, Bookstaver PB, et al. Impact of drug shortages on health system pharmacies in the southeastern united states. Hosp Pharm. 2015;50:279–86.

[50] Wutzler P, De Clercq E, Wutke K, Färber I. Oral brivudin vs. intravenous acyclovir in the treatment of herpes zoster in immunocompromised patients: A randomized double-blind trial. Journal of Medical Virology. 1995 Jul;46(3):252

[51] Patil JM, Hirlekar RS, Gide PS, Kadam VJ. Tre nds in floating drug delivery systems. J Sci Ind Res 2006;65 :1-21.

[52] Kumar R, Philip A. Gastroretentive dosage forms for prolonging gastric residence time. Int J Pharm Med 2007;21 :157 171.

[53] Arora S, Ali J, Ahuja A, Khar RK, Baboota S. F loating drug delivery systems: a review. AAPS PharmSciTech 2005;6 :E372 E390.

[54] Emmert DH, Treatment of common cutaneous Herpes Simplex Virus Infections. Am. Fam. Physician. 2000;61:1697-704.

[55] Madhivanan, Purnima et al. The Epidemiology of Herpes Simplex Virus Type-2 Infection among Married Women in Mysore. India. Am. Sex. Tran. Diseas. Asso. 2007;34(11):935-37.

[56] Tran T, Druce J, Catton MC, Kelly H, Birch CJ. Changing epidemiology of genital herpes simplex virus infection in Melbourne, Australia, between 1980 and 2003. Sex Transm Infect. 2004;80,277 79.

[57] Wadhawan J, Parmar PK, Bansal AK. Nanocrystals for improved topical delivery of medium soluble drug: A case study of acyclovir. Journal of Drug Delivery Science and Technology. 2021 Oct;65:102662.