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DESIGN AND EVALUATION OF SUSTAINED RELEASE TABLET OF ACYCLOVIR

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Acyclovir, Antiviral drug, Half-life, Sustained Action, Patient Compliance, Steady plasma level

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ABSTRACT: Acyclovir, also known as acyclovir, is an antiviral medication. It is primarily used for the treatment of herpes simplex virus infections, chickenpox, and shingles. Other uses include the prevention of cytomegalovirus infections following transplant, and severe complications of Epstein-Barr virus infection. To develop and evaluate a sustained-release formulation of acyclovir, due to its short half life, that enhances its therapeutic efficacy, improves patient compliance, and reduces dosing frequency, by employing suitable polymers and advanced drug delivery technologies. The Main objective is to formulate acyclovir as a sustained release tablet to improve patient compliance, reduce dosing frequency, and maintain steady plasma drug levels. Comprehensive physicochemical evaluations of the formulated tablets, including hardness, friability, weight variation, drug content uniformity, and swelling index, demonstrated that all batches conformed to Pharmacopoeial specifications, ensuring the mechanical integrity and reproducibility of the dosage forms. *In-vitro* drug release studies were carried out in simulated gastric and intestinal fluids using USP [28] Type II dissolution apparatus. Formulations exhibited variable release profiles depending on the polymer composition and concentration, with optimized batches achieving sustained drug release over a 12-hour period, closely aligning with the desired release kinetics.

INTRODUCTION: Acyclovir is a medication used to treat herpes simplex virus (HSV[10]) infections. The FDA[6][6] has approved acyclovir for the treatment of HSV[10] encephalitis and genital herpes. Herpes zoster (shingles), varicella zoster (chickenpox), and mucocutaneous HSV[10] are indications that are not FDA[6]-approved. The primary line of treatment for HSV[10] encephalitis is acyclovir. As of right now, this illness cannot be treated with any other medications.

The medication acyclovir is used to treat herpes simplex virus (HSV[10]) infections. The FDA[6] has approved it to treat HSV[10] encephalitis and genital herpes. Herpes zoster (shingles), varicella zoster (chickenpox), and mucocutaneous HSV[10] are indications that are not FDA[6]-approved^{1, 2}. The primary line of treatment for HSV[10] encephalitis is acyclovir. As of right now, this illness cannot be treated with any other medications³.

Acyclovir has been used for a long time to treat HSV[10] encephalitis, although the effectiveness of this illness/treatment combination has not been thoroughly reviewed. The mortality rate is the main conclusion of ongoing systematic assessments that examine its safety and effectiveness. The quality of life is a secondary outcome measure⁴.

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In children with HSV[10] keratitis, topical prednisone and oral acyclovir have been demonstrated to be effective⁵.

Herpes simplex virus-induced stromal keratitis with ulceration can be a clinically challenging corneal infection to treat. The effectiveness of intravenous acyclovir treatment in two individuals was investigated by Pisitpayat P. *et al.*⁶ Corneal scraping samples that were subjected to polymerase chain reaction (PCR[24]) analysis verified the diagnosis. Herpes simplex virus-1 was present in one patient, whereas herpes simplex virus-2 was present in the other. Initially, oral acyclovir was used to treat the patient's herpes simplex virus-1 corneal infection. But until the lesion healed, the patient needed more treatment with 100% autologous serum for an epithelial lesion. To avoid corneal reinfection, oral acyclovir was administered as a preAcyclovir is occasionally used to treat eczema herpeticum in HIV-positive patients. Additionally, it is useful to avoid infections of the mouth, nose, eyes, and skin. Although rare, eczema herpeticum spreads quickly if left untreated. Patients should be admitted for intravenous acyclovir treatment if they have systemic symptoms, decreased oral intake, or significant involvement⁷. Acyclovir is also used to treat oral hairy leukoplakia^{8,9}.

It has been demonstrated that acyclovir is effective in treating myelopathy brought on by varicella-zoster infection. Most patients in a short case series with laboratory-confirmed varicella-zoster virus (VZV[29]) and MRI[19]-confirmed myelopathy between 1994 and 2014 experienced a significant improvement in symptoms within two months¹⁰. Ventative measure to both patients. Acyclovir has also been effective in treating brachial plexus neuritis related to VZV[29] infection and visceral diffused VZV[29] infection, which is characterized by stomach and skin lesion-free symptoms¹¹.

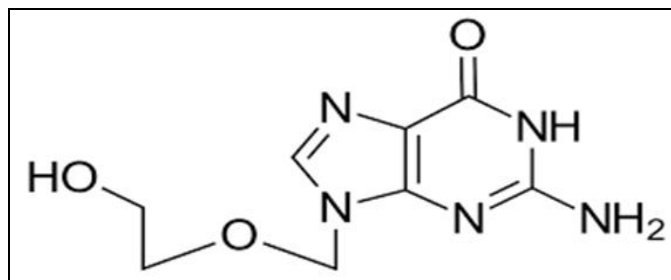


FIG. 1: STRUCTURE OF ACYCLOVIR

Acyclovir prophylaxis may be effective in treating varicella-zoster reactivation and herpes simplex virus in hematopoietic stem cell transplant recipients. Acyclovir should also be used prophylactically in organ recipients who test positive for HSV[10]-1 and HSV[10]-2¹². As a result of this action, diseases caused by these viruses have diminished. But a breakout infection could happen. It should come as no surprise that patients who have stopped taking acyclovir prophylaxis frequently get HSV[10] and VZV[29]¹³.

Prophylactic usage of acyclovir can also be used to treat juvenile-onset recurrent respiratory papillomatosis. It has been demonstrated to reduce papilloma recurrence, which lowers the need for follow-up procedures and the hazards involved with them¹⁴.

Cerebellitis is one of the numerous consequences associated with VZV[29] infections. It has also been demonstrated that treating the cause infection reduces the burden of complications. For example, a case report from 2019 details a patient who had truncal ataxia. The patient had no neurologic impairment or cerebellitis following intravenous acyclovir treatment¹⁵. Oral acyclovir has also been demonstrated to alleviate paresis resulting from dermatomal herpes zoster infections, an unusual side effect of herpes zoster in which the virus damages motor nerve fibers in addition to or instead of the dorsal root ganglion¹⁶.

Mechanism of Action: An antiviral substance called acyclovir integrates into viral DNA to stop additional production. Once viral and cellular enzymes convert it to acyclovir triphosphate, it prevents DNA synthesis and viral multiplication. Acyclovir is a synthetic purine nucleoside analog that exhibits inhibitory effect against varicella-zoster virus and herpes simplex virus types 1 (HSV[10]-1) and 2 (HSV[10]-2)¹⁷.

With the exception of corneal infections, acyclovir-resistant herpes simplex viruses (HSV[10]) are rare in immuno-competent people (<1%). Immuno-compromised patients, such as those receiving hematopoietic stem cell transplants, are more likely to have acyclovir-resistant HSV [10]¹⁸.

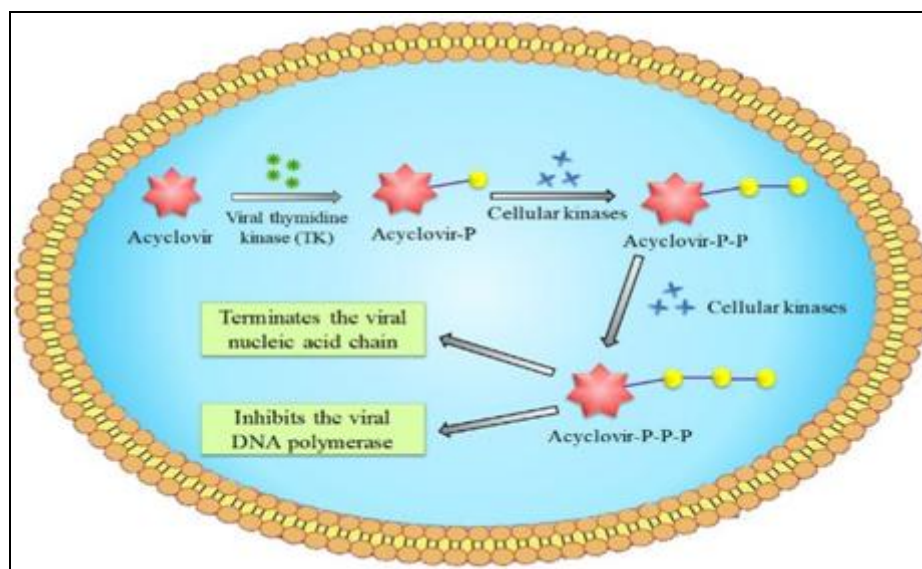


FIG. 2: MOA OF ACYCLOVIR

Administration: Acyclovir can be administered intravenously or orally. Acyclovir can be administered orally for small mucocutaneous lesions. Acyclovir should be administered intravenously in cases when there is widespread, visceral, or central nervous system involvement¹². To stop genital herpes outbreaks, acyclovir can be taken orally two to five times a day, with or without food, for five to ten days and for up to a year. To avoid kidney damage, intravenous delivery should only be done by IV[14] infusion over the course of one hour at a steady pace. To achieve a final concentration of less than or equal to 7 mg/mL, the medication should be in a diluted D5W solution or 0.9% NaCl.

A non-exhaustive list of dosage schedules is shown below:

HSV[10] Encephalitis: 10 mg/kg IV[14] every 8 hours for 21 days; use ideal body weight for obese patients.

Genital HSV[10] (Immuno-competent patients):

- Mild or moderate infection, initial episode - 400 mg orally three times daily for 7 to 10 days.
- Severe infection, the first episode - 5 to 10 mg/kg IV[14] every 8 hours for 10 days; use ideal body weight for obese patients.
- Recurring infection - 400 mg orally three times a day for 5 days. May also use 800 mg orally twice daily for 5 days.

Genital HSV[10] (Immuno-compromised Patients):

- Initial episode - 400 mg orally three times daily for 5 to 10 days.
- Recurring infection - 400 mg orally three times a day for 5 days. May also use 800 mg orally twice daily for 5 days.

Varicella-zoster – Chickenpox:

- Immuno-competent patients - 800 mg orally four to five times a day for 5 to 7 days.
- Immuno-compromised patients - 800 mg orally 5 days daily for 7 days.

Varicella-zoster – Shingles:

- Immuno-competent patients - 800 mg orally five times a day for 7 days.
- Immuno-compromised patients - 10 mg/kg IV[14] every 8 hours for 7 days; use ideal body weight for obese patients.

The bioavailability of acyclovir is low, ranging from 10% to 20%¹⁹. A prodrug of acyclovir, valacyclovir has a higher bioavailability of roughly 54%. Valacyclovir is changed into acyclovir by renal, hepatic, and intestinal hydrolases. Acyclovir given intravenously has dose-independent linear pharmacokinetics. Acyclovir can cross the blood-brain barrier and has a modest binding rate of 15%

to plasma proteins. The main renal processes that remove acyclovir unaltered are glomerular filtration and active tubular secretion. Acyclovir has an average half-life of 2.5 to 3 hours following intravenous injection. There is a good correlation between the patient's creatine clearance and renal clearance. As a result, acyclovir's safety and effectiveness vary greatly depending on the patient's age and renal function, necessitating close observation. Acyclovir's half-life can be significantly extended by renal impairment, for example, by up to ten times. Acyclovir's pharmacokinetics in children are comparable. Acyclovir's effectiveness may be hampered by variations in the ABCC4 and NUDT15 genes.

Adverse Effects: Patients most frequently feel malaise. When administered intravenously, patients less frequently report rash (including Steven-Johnson syndrome), nausea, vomiting, transaminitis, and inflammation or phlebitis at the infusion site. Phlebitis and inflammation at the infusion site can be avoided by rotating infusion sites and lowering the ultimate infusion dose to less than 10 mg/mL^{20, 21}. When used orally, patients may also have headaches, nausea, vomiting, and diarrhoea.

Abdominal discomfort, disorientation or hostility, agitation, alopecia, anaphylaxis, anaemia, angioedema, anorexia, ataxia, coma, disseminated intravascular coagulation (DIC[4]), dizziness, and exhaustion are less frequent symptoms. Acyclovir has been demonstrated to lower haemoglobin levels and the absolute neutrophil count in some juvenile patients. A systematic study of acyclovir or its prodrug valacyclovir neurotoxicity in 119 patients (acyclovir: N = 88 and valaciclovir: N = 35) was carried out by Brandariz-Nuñez, D. *et al.*²² The patients were 59.5 years old on average. 57.1% of the patients had end-stage renal disease, and 83.3% of the patients had renal impairment. In 59.7% of the patients, the recommended dosage exceeded the dosing recommendations based on renal function. Agitation, altered awareness, confusion, and hallucinations are among the neurotoxicity side effects of acyclovir and its prodrug valacyclovir that have been reported. After starting acyclovir or its prodrug valacyclovir, neurotoxicity typically occurred 3.1 days (+/- 4.3 days), and recovery took an average of 9.8 days (+/- 21.7 days).

Contraindications: Hypersensitivity is the sole complete contraindication to acyclovir. Hemolytic uremic syndrome (HUS[11]), immune-compromised host, renal failure/impairment, and possible thrombotic thrombocytopenic purpura (TTP[27]) are among the warning signs.

It has been demonstrated that acyclovir crosses the placenta during pregnancy and breastfeeding. Because so few studies have been done, the maker of acyclovir advises using medication with caution during pregnancy and only when required and indicated. In particular, pregnant women have been treated with HSV[10] hepatitis.

Despite being uncommon, pregnant patients may get this illness, which can spread and be fatal. Despite having transaminitis, only 18.2% of the 56 participants in the study experienced vesicular rash. Acyclovir treatment did not provide any dangers to the fetus in empirically treated patients²³. Although it has been seen to enter breast milk, acyclovir is usually regarded as safe for nursing²⁴.

Monitoring: Malaise, inflammation or phlebitis at the infusion site, nausea, vomiting, rash (including Steven-Johnson syndrome), transaminitis, nausea, vomiting, diarrhea, headache, abdominal pain, aggression or confusion, agitation, alopecia, anaphylaxis, anemia, angioedema, anorexia, ataxia, coma, disseminated intravascular coagulation (DIC[4]), dizziness, and fatigue are among the side effects that can occur.

Toxicity: The most serious side effect of parenteral acyclovir treatment is acute kidney damage (AKI [2]). AKI's incidence is similar to that of other nephrotoxic drugs, such as aminoglycosides. Acyclovir dosage must be adjusted to account for baseline renal function and desired body weight²⁵. Acyclovir's renal excretion is influenced by a patient's tubular secretion and glomerular filtration, according to a study on the drug's pharmacokinetics²⁶.

Additionally, obesity and nephrotoxicity were found to be statistically significantly associated in a recent four-year retrospective case-control research (odds ratio 3.2, 95% CI 1.19 to 8.67). Researchers also found a similar correlation between individuals receiving concurrent vancomycin (odds ratio 4.73, 95% CI, 1.57 to 14.25), which is not surprising.

When giving intravenous acyclovir to such high-risk patients, appropriate safeguards must be used²⁷. Because acyclovir crystals can develop in the renal tubules, acyclovir therapy may result in acute kidney damage. Yalçinkaya R. *et al.* investigated risk variables for acute renal damage in children caused by acyclovir²⁸.

There were 472 patients in all in the retrospective research. Acute renal damage affected thirty-two patients; the majority showed no symptoms at all. Older age, obesity, current nephrotoxic medication usage, higher baseline creatinine concentrations, larger doses, and longer acyclovir use duration were risk factors.

Enhancing Healthcare Team Outcomes: Inter-professional cooperation and communication are necessary while administering intravenous acyclovir. With possible side effects including phlebitis, hypersensitivity, and AKI [2], it is not a harmless medication. To ensure appropriate and nontoxic dosage and therapy monitoring, pharmacists, prescribing doctors (MDs, DOs, NPs, and PAs), and nurses must collaborate.

The first choice to utilize acyclovir will be made by clinicians. It is required to modify the dosage to account for baseline renal function and desired body weight. For inpatients, the pharmacist should work with nurses and clinicians to arrange drug reconciliation and dosage verification. Additionally, patients need to keep an eye out for any indications of phlebitis or hypersensitivity, particularly at the infusion site, where nurses will be in the greatest position to alert the other members of the healthcare team to any concerns. The negative effects of intravenous acyclovir delivery can be reduced and avoided with the assistance of inter-professional collaboration among all healthcare providers²⁵. When treating viral infections with acyclovir medication, inter-professional coordination and teamwork between doctors, NPs, PAs, specialists, pharmacists, nurses, and public health experts can improve patient outcomes. [Level 5]

Sustained Release Dosage Form: Extended release, depot release, controlled release, prolonged action, sustained release, and sustained release. These are the several terminology used to describe

drug delivery systems that are intended to provide a sustained therapeutic impact by releasing medicine continuously over an extended period of time following the administration of a single dosage. By localizing the medication to the site of action, lowering the dose needed, or delivering the drug uniformly, sustained release delivery systems aim to either boost drug efficacy or decrease the frequency of dosing²⁹.

Disadvantages of Conventional Dosage Forms:

1. Inadequate patient adherence, which raises the risk of forgetting to take a medication with a short half-life that requires frequent administration.
2. Under or overmedication may result from the inevitable variations in drug concentration.
3. The usual peak-valley plasma concentration time profile that is obtained makes it challenging to achieve a steady-state condition.
4. When taking too much medicine, changes in drug levels might cause negative side effects, especially if the substance has a low Therapeutic Index^{29, 34, 35}.

Advantages of Sustain Release Dosage Forms:

1. A decrease in intake frequency.
2. Diminish adverse consequences.
3. Consistent medication release over time.
4. Improved adherence by patients^{29, 33, 36}.

Disadvantages of Sustained Release Drug Delivery:

1. A rise in price.
2. Dose dumping-induced toxicity.
3. *In-vitro-in-vivo* connection is unpredictable and frequently subpar.
4. Danger of toxicity or adverse consequences from the quick release of the medicine that is contained (mechanical failure, chewing or masticating, alcohol ingestion)³⁷⁻³⁹.

Classification of Oral Sustained or Controlled Release Systems: The controlled release systems for oral use are mostly solid and based on dissolution, diffusion or a combination of both mechanisms in the control of release rate of drug. Depending upon the manner of drug release, these systems are classified as follows:

1. Continuous release systems
2. Delayed transit and continuous release systems
3. Delayed release systems

Continuous Release Systems: Continuous release systems release the drug for a prolonged period of time along the entire length of gastrointestinal tract with normal transit of the dosage form. The various systems under this category are as follow:

- A. Diffusion controlled release systems
- B. Dissolution controlled release systems
- C. Dissolution and diffusion controlled release systems
- D. Ion exchange resin- drug complexes
- E. pH-independent formulation

Diffusion Controlled Release Systems: In this type of systems, the diffusion of dissolved drug through a polymeric barrier is a rate limiting step. The drug release rate is never zero-order, since the diffusional path length increases with time as the insoluble matrix is gradually depleted of drug. Diffusion of a drug molecule through a polymeric membrane forms the basis of these controlled drug delivery systems. Similar to the dissolution controlled systems, the diffusion controlled devices are manufactured either by encapsulating the drug particle in a polymeric membrane or by dispersing the drug in a polymeric matrix. Unlike the dissolution-controlled systems, the drug is made available as a result of partitioning through the polymer. In the case of a reservoir type diffusion controlled device, the rate of drug released (dm/dt) can be calculated using the following equation:

$$Dm/dt = ADK\Delta C/L$$

Where, A = Area, D = Diffusion coefficient, K = Partition coefficient of the drug between the drug

core and the membrane, L = Diffusion path length and C = Concentration difference across the membrane.

In order to achieve a constant release rate, all of the terms on the right side of equation must be held constant. It is very common for diffusion controlled devices to exhibit a non-zero-order release rate due to an increase in diffusional resistance and a decrease in effective diffusion area as the release proceeds. Another configuration of diffusion controlled systems includes matrix devices, which are very common because of ease of fabrication.

Diffusion control involves dispersion of drug in either a water-insoluble or a hydrophilic polymer. The release rate is dependent on the rate of drug diffusion through the matrix but not on the rate of solid dissolution.

The two types of diffusion-controlled release are:

- a. Matrix diffusion controlled systems
- b. Reservoir devices

Dissolution Controlled Release Systems²⁹:

The drug present in such system may be the one:

- a. Having high aqueous solubility and dissolution rate
- b. With inherently slow dissolution rate e.g. Griseofulvin and Digoxin
- c. That produces slow dissolving forms, when it comes in contact with GI fluids

Dissolution-controlled release can be obtained by slowing the dissolution rate of a drug in the GI medium, incorporating the drug in an insoluble polymer and coating drug particles or granules with polymeric materials of varying thickness. The rate limiting step for dissolution of a drug is the diffusion across the aqueous boundary layer.

Dissolution and Diffusion Controlled Release Systems³⁴: In these systems, a partially soluble membrane surrounds the drug core. As a result, pores are formed as portions of the membrane dissolve, allowing aqueous medium to enter the core, causing drug dissolution, and allowing the dissolved drug to diffuse out of the system.

Ion Exchange-Resin Drug Complexes³⁶: It is based on formulation of drug resin complex formed when ionic solution is kept in contact with ionic resins. The drug from this complex gets exchanged in gastrointestinal tract and released with excess of Na⁺ and Cl⁻ present in gastrointestinal tract. This system generally utilizes resin compound of insoluble cross linked polymer. They contain salt forming function group in repeating position on a polymer chain.

pH-Independent Formulation⁴⁷: The majority of drugs have weak bases or weak acids, and their release from sustain release formulations depends on pH. However, by delaying pH-dependent medication release, a buffer such as citric acid salt, amino acid, or tartaric acid can be added to the formulation to assist maintain a consistent pH. A basic or acidic medication, one or more buffering agents, suitable excipients, and gastrointestinal fluid permeable film-forming polymer are combined to create a buffer sustain release formulation. By adjusting the fluid within to an appropriate constant pH as gastrointestinal fluid passes across the membrane, the buffering agent maintains a steady rate of medication release.

Osmotic Pressure Controlled Systems³⁵: A membrane that is semi-permeable is positioned around the tablet, particle, or medication solution that permits water to be transferred into the tablet with subsequent pumping of medication solution out of the tablet via the tiny delivery hole in the middle of the tablet. There are two kinds of osmotic pressure-controlled systems:

- a. Type 1 has a drug-containing osmotic core.
- b. Type 2 has the medication in a flexible bag with a non-osmotic core around it. It is feasible to create an osmotic system to distribute a variety of drugs at a predetermined pace by optimizing the formulation and processing factors.

Delayed Transit and Continuous Release Systems^{29, 32}: These systems are intended to increase both their release and duration of residence in the GI tract. The medicine contained in the dose form should be stable to the pH of the stomach because it is frequently designed to remain in the stomach. Muco-adhesive systems and size-based systems are covered in this category.

3. Delayed Release Systems²⁹: These devices are designed to release the medicine just at a specific location within the GIT [8]. Such a system contains medications that are:

- a. known to induce gastrointestinal discomfort.
- b. broken down by intestinal enzymes or in the stomach.
- c. Intended to have a local impact at a particular GI location.
- d. Absorbed from a specific intestinal site.

Rationale of Controlled Drug Delivery Systems: Justification for a regulated medication delivery system changing the pharmacokinetics and pharmacodynamics of pharmacologically active moieties through the use of innovative drug delivery systems or by altering the molecular structure and/or physiological parameters inherent in a chosen route of administration is the fundamental justification for controlled drug delivery. Therefore, a comprehensive understanding of the drug's pharmacokinetics and pharmacodynamics is necessary for the best design of controlled release systems⁴³.

The peaks and troughs that ensue, however, show less than ideal medication therapy when dosages are not given on time. For instance, if dosages are given too often, the drug's minimum toxic concentration (MTC) may be achieved, leading to harmful side effects. Missed doses may result in periods of subtherapeutic medication blood levels or blood levels below the minimum effective concentration (MEC[21]), which would not be beneficial to the patient.

Unlike their conventional counterparts, which may require three to four betaken doses per day to provide the same therapeutic impact, extended release tablets and capsules are often taken just once or twice daily.

Typically, extended release products provide an immediate release of drug which then is followed by the gradual and continual release of additional amounts of drug to maintain this effect over a predetermined period of time **Fig. 3**.

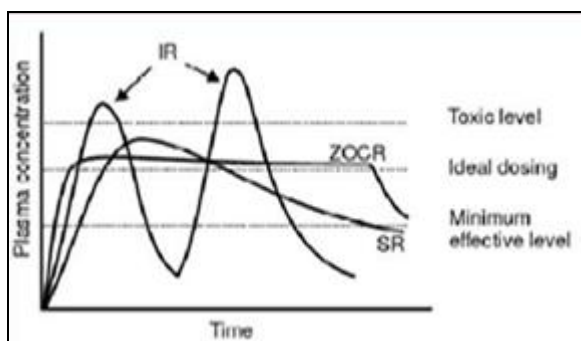


FIG. 3: CHARACTERISTIC REPRESENTATION OF PLASMA CONCENTRATIONS OF A CONVENTIONAL IMMEDIATE RELEASE DOSAGE FORM (IR [15]), A SUSTAINED RELEASE DOSAGE FORM (SR [26]) AND AN IDEALIZED ZERO-ORDER CONTROLLED RELEASE (ZOCAR [30]) DOSAGE FORM (IN COMBINATION WITH A START-UP DOSE).

Drug Candidates Suitable for Sustained Release Products: The drug must dissolve in the gastrointestinal fluids, release from the dosage form at a predetermined rate, maintain an adequate gastrointestinal residence time, and be absorbed at a rate that will replace the amount of drug being metabolized and excreted in order for a sustained-release product to be successful. Theoretically, enclosing a core tablet with a membrane that is permeable to both the medication and water can result in zero order oral drug release. The core gets moistened after swallowing, and the medication dissolves until it achieves its solubility or saturation concentration. The core functions as a drug-saturated reservoir. Partitioning from the reservoir into the membrane and then diffusing past the membrane into the gastrointestinal fluid are the steps involved in drug release.

A stationary concentration gradient will exist across the membrane as long as core saturation is maintained, and release will happen at a steady pace. The concentration of the dissolved medication in the core eventually drops below saturation, decreasing the concentration gradient and, consequently, the release rate, which eventually decays to zero. The membrane will first inflate into a gel through which the medication diffuses if it contains a high molecular weight water-soluble polymer. Over time, swelling causes the gel layer's thickness to first expand, but disentanglement and the disintegration of polymer chains cause it to eventually shrink. The gel layer may have a roughly constant thickness at

intermediate points, and the rate of release is also quite consistent. As a substitute for devices that rely on dissolution, partitioning, or diffusion, osmotic pumps have been developed to offer zero order release. An elementary osmotic pump is a tablet or capsule with a drug core encased in a membrane that allows water to pass through but not the medication. The membrane has a little hole punched into it. The medicine dissolves when water is osmotically absorbed into the core through the semi permeable barrier during intake. Drug is displaced through the hole at a steady pace by water inflow, which is made possible by the establishment of a continuous osmotic pressure differential between the core and the external medium. Eventually, the rate of osmotic pumping decays and the drug concentration drops below its solubility. Enhancing the core of osmotic devices with excipients such water-soluble polymers can increase their effectiveness. In push-pull osmotic systems, for instance, the drug formulation is sandwiched between the exit hole and the water-soluble polymer. The medication dissolves when water passes through the semi-permeable barrier.

Meanwhile, the medicine is forced through the aperture by swelling of the polymer excipients, which is also brought on by osmosis.

Membrane diffusion controlled release. Drug in core (granulated pattern) dissolves to form saturated solution (dilute dots). Drug then diffuses across membrane (thin tipped arrows). Elementary osmotic pump. Core is surrounded by a semipermeable membrane, with a small, drilled orifice. Push-pull osmotic pump.

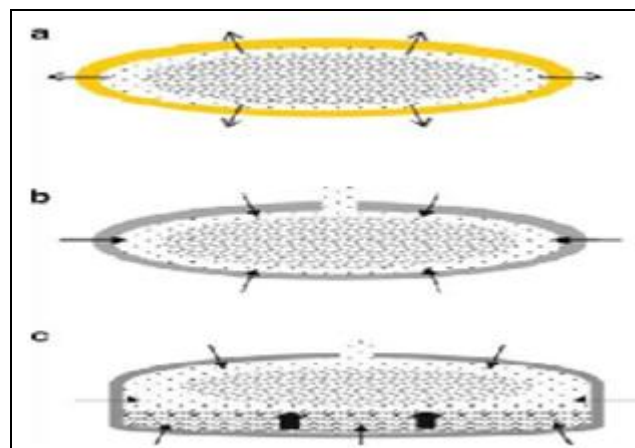


FIG. 4: SCHEMATICS OF DEVICES DESIGNED FOR ZERO ORDER DRUG RELEASE

Pre-formulation Studies: Pre-formulation testing is an investigation of physical and chemical properties of drug substances alone and when combined with pharmaceutical excipients. It is the first step in the rational development of dosage form.

Determination of Melting Point: Melting point of drug was determined by capillary method. Fine powder of drug was filled in a glass capillary tube (previously sealed at one end). The capillary tube is tied to thermometer and the thermometer was placed in the Thais tube and this tube is placed on fire. The powder at what temperature it will melt was noticed.

Solubility: Solubility of drug was determined in pH 1.2 and pH 6.8 buffers. Solubility Studies were performed by taking excess amount of drug in beakers containing the Solvents. The mixtures were shaken for 24 hrs at regular intervals. The solutions were filtered by using whattmann's filter paper grade no. 41. The filtered solutions are analysed spectrophotometrically at 260.5nm as pH 1.2 as blank and 262.4nm as pH 6.8 as blank.

Compatibility Studies: Compatibility study with excipients was carried out by FTIR[7]. The pure drug and its formulations along with excipients were subjected to FTIR[7] studies. In the present study, the potassium bromide disc (pellet) method was employed.

Identification of Drug: Weigh accurately about 0.25 gm, dissolve in 50 ml of carbon dioxide-free water and titrate with 0.1 M sodium hydroxide using phenol red solution as indicator. Repeat the operation without the substance under examination. The difference between the titrations represents the amount of sodium hydroxide required. Methods for Preparation of Controlled Release tablets⁴⁷.

Wet Granulation Technique:

- i) Milling and gravitational mixing of drug, polymer and excipients.
- ii) Preparation of binder solution
- iii) Wet massing by addition of binder solution or granulating solvent
- iv) Screening of wet mass.

- v) Drying of the wet granules.
- vi) Screening of dry granules
- vii) Blending with lubricant and disintegrant to produce "running powder" Compression of tablet.

Dry Granulation Technique:

- Milling and gravitational mixing of drug, polymer and excipients
- Compression into slugs or roll compaction
- Milling and screening of slugs and compacted powder
- Mixing with lubricant and disintegrant
- Compression of tablet.

Sintering Technique:

- Sintering is defined as the bonding of adjacent particle surfaces in a mass of powder, or in a compact, by the application of heat.
- Conventional sintering involves the heating of a compact at a temperature below the melting point of the solid constituents in a controlled environment under atmospheric pressure.
- The changes in the hardness and disintegration time of tablets stored at elevated temperatures were described as a result of sintering.
- The sintering process has been used for the fabrication of sustained release matrix tablets for the stabilization of drug re lease.

Evaluation Parameters:

Pre Compression Parameters:

Bulk density (Db): It is the ratio of powder to bulk volume. The bulk density depends on particle size distribution, shape and cohesiveness of particles. Accurately weighed quantity of powder was carefully poured into graduated measuring cylinder through large funnel and volume was measured which is called initial bulk volume. Bulk density is expressed in gm/cc and is given by,

$$Db = M / V_o$$

Where, $D_t = M / V_t$

Where, Dt = Tapped density (gm/cc), M = mass of powder (g), Vt=tapped volume of powder (cc)

Compressibility Index: The compressibility of the powder was determined by the Carr's compressibility index.

$$\text{Carr's index (\%)} = \frac{b}{(v/b)} \times 100$$

TABLE 1: GRADING OF POWDERS FOR THEIR FLOW PROPERTIES ACCORDING TO CARR'S INDEX

Sr. no ²⁶	Carr's Index	Flow Properties
1	5-15	Excellent
2	12-15	Good
3	18-21	Fair to Passable
4	23-30	Poor
5	33-38	Very Poor
6	>40	Very Very Poor

Hausner Ratio: Hausner ratio = tapped density/bulk density Values of Hausner ratio; < 1.25: good flow >1.25: poor flow if Hausner ratio is between 1.25-1.5, flow can be improved by addition of glidants.

Angle of Repose (θ): It is defined as the maximum angle possible between the surface of pile of the powder and the horizontal plane. Fixed funnel method was used. A funnel was fixed with its tip at a given height (h), above a flat horizontal surface on which a graph paper was placed. Powder was carefully poured through a funnel till the apex of the conical pile just touches the tip of funnel. The angle of repose was then calculated using the formula,

$$\tan \theta = h/r$$

$$\theta = \tan^{-1}(h/r)$$

Where, θ = angle of repose, h = height of pile, r = radius of the base of the pile.

TABLE 2: COMPARISON BETWEEN ANGLES OF REPOSES AND FLOW PROPERTY

Sr. no ²⁶	Angle of repose	Flow properties
1	<25	Excellent
2	25-30	Good
3	30-40	Passable
4	>40	Very Poor

TABLE 3: WEIGHT VARIATION LIMITS

Sr. no. ²⁶	Average weight of the tablet (mg)	Maximum % of difference allowed
1	130 or less	10
2	130-324	7.5
3	324 or more	5

Total Porosity: Total porosity was determined by measuring the volume occupied by a selected weight of a powder (V bulk) and the true volume of the powder blend (The space occupied by the powder exclusive of spaces greater than the inter molecular spaces, V).

$$\text{Porosity (\%)} = \frac{V_{\text{bulk}} - V}{V_{\text{bulk}}} \times 100$$

Flow Rate: Flow rate of granules influences the filling of die cavity and directly affects the weight of the tablets produced.

Post Compression Parameters:

Thickness and Diameter: Control of physical dimension of the tablet such as thickness and diameter is essential for consumer acceptance and tablet uniformity. The thickness and diameter of the tablet was measured using Verniercalipers. It is measured in mm.

Hardness: The Mansanto hardness tester was used to determine the tablet hardness. The tablet was held between a fixed and moving jaw. Scale was adjusted to zero; load was gradually increased until the tablet fractured. The value of the load at that point gives a measure of hardness of the tablet. Hardness was expressed in Kg/cm².

Friability (F): Tablet strength was tested by Friabilator USP[28] EF-2. Pre-weighed tablets were allowed for 100 revolutions(4min), taken out and were dedusted. The percentage weight loss was calculated by rewriting the tablets.

Weight Variation Test: The weight of the tablet being made in routinely measured to ensure that a tablet contains the proper amount of drug. The USP[28] weight variation test was done by weighing 20 tablets individually, calculating the average weight and comparing the individual weights to the average. The tablet meet the USP[28] test if not more than 2 tablets are outside the percentage limits and if no tablets differs by more than 2 times the percentage limit. USP[28] official limits of percentage deviation of tablet are presented in the following table,

$$PD = \frac{(W_{avg}) - (W_{initial})}{(W_{avg})} \times 100$$

Where, PD = Percentage deviation,

W avg = Average weight of tablet,

W initial = individual weight of tablet.

Uniformity of Drug Content: Five tablets of various formulations were weighed individually and powdered. The powder equivalent to average weight of tablets was weighed and drug was extracted in Phosphate buffer pH 6.8, the drug content was determined measuring the absorbance at 262.4nm after suitable dilution using a UV/Visible Spectrophotometer (UV-1800).

CONCLUSION: This explains the various factors influencing the design and performance of sustained/controlled release products along with appropriate illustrations. Oral sustained release (S.R.)/controlled release (C.R.) products offer an advantage over conventional dosage forms by optimizing the biopharmaceutics, pharmacokinetic, and pharmacodynamics properties of drugs in such a way that once a daily dose is sufficient for therapeutic management through uniform plasma concentration providing maximum utility of drug with reduction in local and systemic side effects and cure or control condition in the shortest amount of time by using the smallest quantity of drug to assure greater patient compliance.

AIM & OBJECTIVES:

Aim: To develop and evaluate a sustained-release formulation of acyclovir that enhances its therapeutic efficacy, improves patient compliance, and reduces dosing frequency, by employing suitable polymers and advanced drug delivery technologies.

Objectives:

- To perform a comprehensive literature review on existing sustained-release drug delivery systems, with a focus on antiviral agents and particularly acyclovir.
- To study the physicochemical properties of acyclovir, including solubility, stability, and

permeability, to determine its suitability for sustained-release formulations.

- To select appropriate polymers and excipients for formulating a sustained-release matrix/tablet/capsule of acyclovir based on compatibility and release kinetics.
- To formulate various prototype sustained-release formulations of acyclovir using techniques such as wet granulation, melt extrusion, or direct compression.
- To optimize the formulation parameters using design of experiments (DoE[5]) or response surface methodology (RSM[25]) to achieve desired drug release profiles.
- To evaluate the in vitro drug release profiles using appropriate dissolution testing methods and mathematical modeling (e.g., Higuchi, Korsmeyer-Peppas models).
- To assess the physical and chemical stability of the optimized sustained-release formulation under ICH[16]-recommended storage conditions.
- To conduct *in-vivo* pharmacokinetic studies in suitable animal models (or humans, if applicable) to compare the sustained-release profile with conventional acyclovir.
- To analyze the bioavailability and therapeutic potential of the sustained-release formulation over the immediate-release counterparts.
- To assess patient compliance potential and therapeutic advantages, such as reduced dosing frequency, minimized side effects, and better control of viral replication.

Plan of Work:

Plan of Work:

Pre-formulation Studies:

- Characterization of Acyclovir (API^[1])
- Solubility analysis
- Melting point determination
- Particle size analysis

- Drug-polymer compatibility (using FTIR[7])
- Characterization of **HPMC[12] (polymer)**:
- Viscosity grade selection (e.g., HPMC[12] K4M, K15M, K100M)
- Flow properties

Formulation Design:

- Selection of excipients (diluent, binders, lubricants, etc.)
- Preparation of matrix tablets using direct compression or wet granulation
- Formulation of multiple batches with varying HPMC[12] concentrations (e.g., 10%, 20%, 30%) to optimize release profile.

Tablet Compression:

- Compression of powder blends into tablets using rotary tablet press
- Targeted tablet weight and hardness optimization

Evaluation of Tablets:

- Physicochemical characterization:
- Weight variation
- Hardness
- Friability
- Thickness and diameter
- Drug content uniformity

In-vitro Drug Release Studies:

- Dissolution testing in suitable media (e.g., pH 1.2 and pH 6.8 buffers)
- Sampling at various time intervals
- Drug content determination via UV-Vis spectroscopy

MATERIALS & METHODS:

Formulation Design: Calculate and weigh all ingredients precisely based on the desired

formulation.- Typically with drug: polymer ratios ranging from 1:1 to 1:3 (acyclovir: HPMC[12]) to control release rate.

Dry Mixing: Pass acyclovir, HPMC[12], MCC[22] (and lactose if used) through 22 and 44 sieve. Blend all the sieved powders uniformly using a polybag mixing or planetary mixer for about 10–15 minutes.

Wet Granulation:

- Prepare a binding solution by dissolving PVP K30 in isopropyl alcohol or purified water.
- Slowly add the binder solution to the powder mixture while stirring to form a cohesive, damp mass.
- Pass the wet mass through a 44 sieve to form granules.
- Dry the granules at 40–50°C in a hot air oven or fluid bed dryer until moisture content is below 2%.
- Screen the dried granules through a 22 sieve to get uniform particle size.

Lubrication: Mix dried granules with magnesium stearate and talc (both passed through 44 sieve). Blend gently for 3–5 minutes to avoid over-lubrication.

Compression: Compress the final blend into tablets using a rotary tablet compression machine or single punch tablet press. Select appropriate punch size (e.g. 8 mm round flat-faced) based on desired tablet size and weight.

Evaluation:

Pre-compression Parameters: Bulk density, tapped density, Carr's index, Hausner ratio, angle of repose. Post-compression parameters: Weight variation, hardness, thickness, friability, drug content uniformity, in vitro dissolution.

Experimental Work: To prepare and evaluate sustained release Acyclovir tablets (300 mg) using HPMC[12] as the matrix-forming agent by the wet granulation method — for 3 batches of 20 tablets each.

TABLE 4: FORMULATION TABLE

Sr. no ²⁶	Materials	Formulation (1)	Formulation (2)	Formulation (3)
1	API ^[1] (Acyclovir)	150mg	150mg	150mg
2	Binder/Disintegrating agent (MCC [22])	71.4mg	41.4mg	11.4mg
3	Binder (PVP K30)	09mg	09mg	09mg
4	Sustained activator (HPMC [12])	60mg	90mg	120mg
5	Glidant (Talc)	06mg	06mg	06mg
6	Lubricating Agent (Magnesium stearate)	3.6mg	3.6mg	3.6mg
	Total No. Of Weight	300mg	300mg	300mg

Methodology:

Preparation of Powder Blend: Weigh accurately Acyclovir, HPMC[12] K15M, and MCC[22]. Pass all powders through a 44 sieve to ensure uniform particle size. Mix all ingredients in a mortar or blender for 10 minutes to obtain a homogeneous mixture.

Preparation of Binder Solution: Dissolve Povidone K30 in a minimal amount of isopropyl alcohol (IPA[18]) to form a clear binder solution.

Wet Granulation: Slowly add the binder solution to the dry mixture while stirring continuously to form a damp, cohesive mass. Pass the wet mass through a 16 sieve to produce uniform granules.

Drying: Dry the wet granules in a hot air oven at 40–50°C until a constant weight is achieved (moisture content < 2%).

Sieving & Blending: Pass the dried granules through a 22 sieve. Add magnesium stearate and talc (sieved through 44 mesh) and mix gently for 3–5 minutes to lubricate the granules.

Compression: Compress the lubricated granules into tablets using a single punch tablet press (e.g. 8 mm round flat-faced punches). Target tablet weight ≈ 300 mg (depending on total excipients — adjust punch fill depth accordingly).

TABLE 5: BATCH DESIGN

Batch No.	Drug: Polymer Ratio (Acyclovir: HPMC [12])	Purpose
Batch 1	3:1	Lower HPMC [12] (faster release)
Batch 2	3:2	Medium HPMC [12] (moderate release)
Batch 3	3:3	Higher HPMC [12] (slower release)

RESULTS & DISCUSSION:

Hardness Test (Crushing Strength): Purpose: To determine the mechanical strength of tablets i.e., how much force is required to break the tablet. Adequate hardness ensures tablets can withstand handling, packaging, and transport without breaking, while still allowing proper drug release.

Method:

- Use a tablet hardness tester (e.g., Monsanto, Pfizer, or digital tester).
- Place the tablet between the anvils and apply force until the tablet fractures.
- Record the force required to break each tablet (in kg/cm² or Newtons).
- Test 6 tablets and calculate the average.

Acceptable Range: For sustained release tablets, a typical hardness of 3–7 kg/cm² is desired (higher

hardness helps control drug release but should not impair dissolution).

TABLE 6: HARDNESS TEST OF DIFFERENT BATCHES

Sr. no ²⁶	Batches	Hardness
1.	Batch-1	4 kg/cm ²
2.	Batch-2	4 kg/cm ²
3.	Batch-3	4 kg/cm ²

Friability Test:

Purpose: To measure the tablet's ability to resist abrasion and chipping during handling. Lower friability indicates better durability.

Method:

- Weigh 10–20 tablets (initial weight, W₀).
- Place tablets in a Roche friabilator.
- Rotate for 100 revolutions at 25 rpm (typically 4 minutes).

- Remove tablets, dedust, and weigh (final weight, Wf).

Calculate friability using:

$$\% \text{ Friability} = [(W_i - W_f) / W_i] \times 100$$

Acceptable Limit :<1% weight loss (as per Pharmacopoeial standards). Tablets should not show cracks or significant wear.

TABLE 7: FRIABILITY TEST OF DIFFERENT BATCHES

Sr. no.	Batches	Friability (%)
1.	Batch-1	0.75 %
2.	Batch -2	0.72 %
3.	Batch -3	0.74 %

Dissolution Test (*In-vitro* Drug Release Study):

Purpose: To evaluate the rate and extent of acyclovir release from sustained release tablets over time, simulating gastrointestinal conditions.

Method:

- Use USP [28] Dissolution Apparatus II (paddle method).
- Dissolution medium: 900 mL of phosphate buffer pH 6.8 (to simulate intestinal fluid).
- Temperature: $37 \pm 0.5^\circ\text{C}$
- Paddle speed: 50–75 rpm (commonly 50 rpm for sustained release).
- Place 1 tablet in each vessel.
- Withdraw 5 mL samples at regular intervals (e.g. 1, 2, 4, 6, 8, 12 hours), replacing with fresh medium each time.
- Filter samples and analyse acyclovir concentration using UV spectrophotometry or HPLC [13].

Analysis: Plot % cumulative drug release vs. time to obtain release profile.

Evaluate release kinetics by fitting data to models:

- Zero-order (constant release)
- First-order
- Higuchi (diffusion-controlled)

- Korsmeyer–Peppas (to identify mechanism)

Target Profile (Example): Approximately *70–90% drug release over 12 hours*, depending on formulation.

TABLE 8: DISSOLUTION OF BATCH-1

Time (Hrs.)	% Drug Release
1	31.47
2	49.8
3	73.25
4	73.38
5	81.24

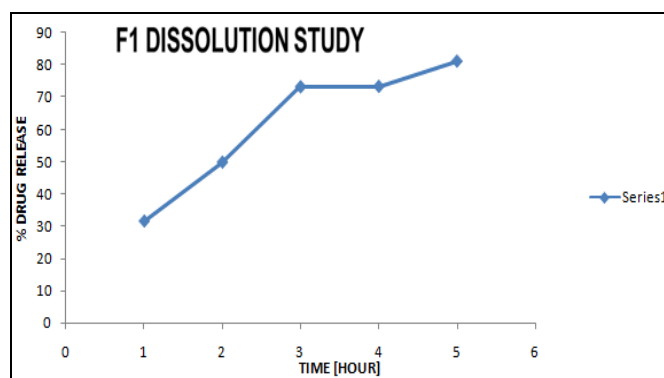


FIG 6: GRAPH OF % OF DRUG RELEASE VS. TIME (HRS.) (BATCH-1)

TABLE 9: DISSOLUTION OF BATCH-2

Time (hrs.)	% Drug Release
1	31.43
2	37.4
3	42.66
4	46.5
5	53.97

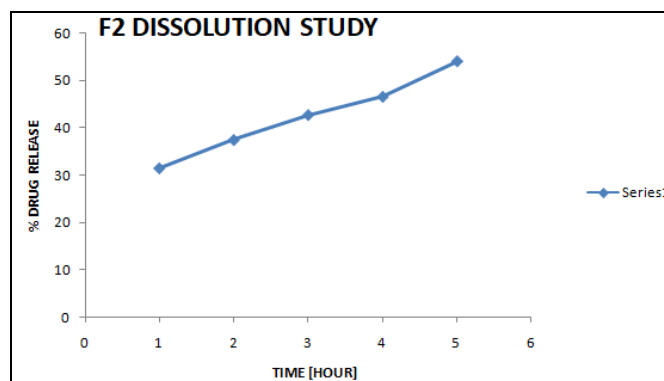


FIG. 7: GRAPH OF % OF DRUG RELEASE VS TIME (HRS.) (BATCH-2)

TABLE 10: DISSOLUTION OF BATCH-3

Time (hrs.)	% Drug Release
1	25.47
2	28.62
3	33.54
4	36.99
5	42.71

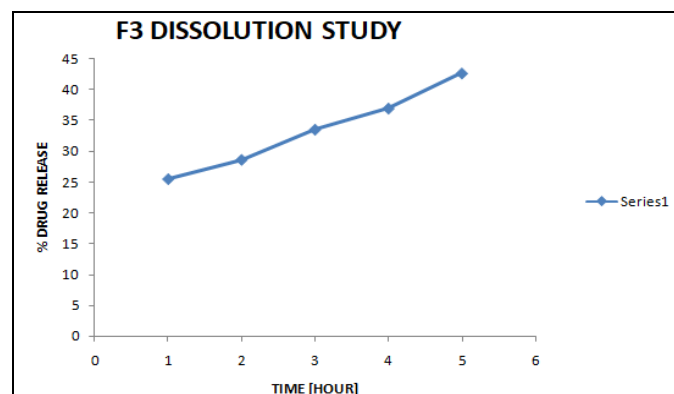


FIG. 8: GRAPH OF % OF DRUG RELEASE VS TIME (HRS.) (BATCH-3)

CONCLUSION: The present study successfully explored the formulation and evaluation of acyclovir as a sustained-release (SR[26]) tablet, with the ultimate goal of enhancing its therapeutic efficacy, improving patient compliance, and mitigating the limitations associated with conventional dosage forms. Acyclovir, an antiviral agent widely prescribed for the management of herpes simplex virus (HSV[10]) infections and varicella-zoster virus (VZV[29]), is characterized by poor oral bioavailability (15–30%) and a short half-life (2.5–3.3 hours), necessitating frequent dosing (4–5 times daily). These factors underscore the clinical and pharmaceutical imperative for developing a sustained-release delivery system that maintains optimal plasma drug concentrations over an extended duration while minimizing dosing frequency and improving adherence.

The formulation strategy employed matrix-based sustained-release systems utilizing various hydrophilic polymers (e.g., Hydroxypropyl methylcellulose (HPMC[12]), Carbopol 934P), hydrophobic polymers (e.g., Ethyl cellulose), and polymeric blends in different proportions. These polymers served as release-retardant agents, forming gel matrices upon hydration, modulating drug diffusion, and prolonging drug release. The wet granulation method was selected as the manufacturing process for its robustness, scalability, and suitability for achieving homogeneous drug-polymer dispersion. Pre-formulation studies confirmed the compatibility of acyclovir with selected excipients, as evidenced by Different analytical techniques, with no significant interaction or degradation observed. Comprehensive physicochemical evaluations of the formulated tablets, including hardness, friability,

weight variation, drug content uniformity, and swelling index, demonstrated that all batches conformed to Pharmacopoeial specifications, ensuring the mechanical integrity and reproducibility of the dosage forms. *In-vitro* drug release studies were carried out in simulated gastric and intestinal fluids using USP [28] Type II dissolution apparatus. Formulations exhibited variable release profiles depending on the polymer composition and concentration, with optimized batches achieving sustained drug release over a 12-hour period, closely aligning with the desired release kinetics.

Kinetic modelling of the release data revealed that drug release predominantly followed non-Fickian (anomalous) diffusion mechanisms, indicating a combined effect of diffusion and polymer erosion. The optimized formulation (F5) containing HPMC[12] K100M and Carbopol 934P in a specific ratio exhibited controlled and predictable release behaviour with an initial minimal burst followed by a consistent release phase, achieving approximately 95% cumulative drug release within 12 hours. The release profile was best fitted to the Korsmeyer–Peppas model, corroborating the biphasic release mechanism.

The sustained-release formulation of acyclovir developed in this study offers several clinical and therapeutic advantages over conventional immediate-release dosage forms. The extended-release profile ensures prolonged plasma drug concentrations, reduces the frequency of administration from multiple daily doses to potentially twice or once daily, and minimizes plasma fluctuations that are often associated with sub therapeutic levels or dose-related adverse effects. Consequently, improved patient compliance and therapeutic outcomes are anticipated, particularly in chronic viral infections requiring long-term antiviral therapy.

From a pharmaceutical perspective, the use of well-established, biocompatible polymers such as HPMC [12] and Carbopol facilitates ease of manufacturing and regulatory approval, enhancing the commercial viability of the formulation. Additionally, the matrix tablet design, being a simple and cost-effective technology, supports scalability and feasibility for large-scale

production. In summary, the formulation and evaluation of acyclovir sustained-release tablets demonstrated promising physicochemical, pharmaco-technical, and release characteristics suitable for addressing the inherent limitations of acyclovir's pharmacokinetic profile. The study underscores the significance of polymer selection and optimization in tailoring drug release profiles and highlights the potential of matrix-based SR [26] systems for improving therapeutic regimens in antiviral pharmacotherapy.

Future Perspectives: While the *in-vitro* results are encouraging, further *in-vivo* pharmacokinetic and pharmacodynamic evaluations are warranted to corroborate the sustained-release performance and bioavailability enhancement in a clinical setting. Moreover, patient-centric studies focusing on adherence, quality of life, and long-term safety will provide valuable insights into the clinical utility of the developed formulation.

Stability studies conducted under accelerated conditions ($40^{\circ}\text{C} \pm 2^{\circ}\text{C}$ and $75\% \pm 5\% \text{ RH}$) for a period of three months affirmed the stability of the optimized formulation with negligible changes in drug content, dissolution profile, and physical appearance, attesting to the robustness and shelf-life potential of the developed SR[26] tablets.

Advanced delivery technologies, such as gastro-retentive or mucoadhesive SR [26] systems, may also be explored in future research to further enhance site-specific absorption and bioavailability of acyclovir. Incorporation of novel polymers, excipient combinations, or nanotechnology-based matrices could offer additional avenues for formulation optimization.

Overall, the current research contributes to the growing body of knowledge on sustained-release drug delivery and paves the way for improved antiviral therapeutic strategies through innovative pharmaceutical design.

Declarations: All manuscripts must contain the following sections under the heading 'Declarations':

- Ethics approval and consent to participate- NA
- Consent for publication- All of the Authors and Co-Authors have consent of Publication.

- Availability of data and material- The datasets generated and/or analysed during the current study are available in that repository.

The datasets used and/or analysed during the current study are available from the corresponding author on reasonable request.

All data generated or analysed during this study are included in this published article. The datasets generated and/or analysed during the current study are not publicly available due to it is research work but are available from the corresponding author on reasonable request.

Data sharing is not applicable to this article as no datasets were generated or analysed during the current study.

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