DRUG AND EXCIPIENTS PROFILE
4.1 Acyclovir

4.1.1 Physico-chemical properties

Acyclovir is an acyclic nucleoside analogue, and it is incorporated into viral DNA inside an infected cell where it interferes with viral replication.

The first new drug application for acyclovir was filed in 1981, and it was first approved for general systemic clinical use in the United Kingdom and the USA in 1982 (King, 1988). By 1988, acyclovir had been licensed in more than 40 countries, and it was estimated that intravenous and oral preparations had already been used in over 10 million courses of treatment (Tilson, 1988). Acyclovir was the first specific antiviral drug to become widely used against herpes viruses, particularly Herpes Simplex Viruses (HSV) types I and II and Varicella Zoster. It is widely used in the treatment of various ocular viral diseases (Jabs, 1998). Acyclovir is a white powder consisting of elongated rectangular crystals; it is prepared by chemical synthesis.

4.1.1.1 Chemical abstract service reg. no.

59277-89-3

4.1.1.2 Chemical name

2-Amino-1, 9-dihydro-9-((2-hydroxyethoxy) methyl)-6H-purin- 6-one. Its chemical structure is depicted in Figure 4.1

![Chemical structure of acyclovir](image.png)

Figure 4.1: Chemical structure of acyclovir

4.1.1.3 IUPAC systematic name

9-((2-Hydroxyethoxy) methyl) guanine

4.1.1.4 Synonyms

Aciclovir; ACV; acycloguanosine; BW-248U; 9-(2-hydroxyethoxymethyl) guanine
4.1.1.5 Molecular formula
C$_8$H$_{11}$N$_5$O$_3$

4.1.1.6 Molecular weight
225

4.1.1.7 Category
Anti-Viral

4.1.1.8 Synthesis
Acyclovir can be prepared by alkylating guanine with 2-(chloromethoxy) ethyl benzoate and hydrolyzing the resulting ester to acyclovir (Gennaro, 1995). Approximately 7.5 tonnes of acyclovir were produced worldwide in 1984 and production has increased significantly since then.

4.1.1.9 Solubility
Acyclovir is slightly soluble in water, insoluble in ethanol, practically insoluble in most organic solvents; soluble in dilute aqueous solutions of alkali hydroxides and mineral acids. Solubility of acyclovir is defined as 2.5 mg/ml at 37°C (< 1 in 400) in water, (< 1 in 5000) in ethanol.

4.1.1.10 Melting Point
256.5°C to 257°C

4.1.1.11 Analytical Profile
Various methods for the identification and quantitative estimation of acyclovir in pharmaceutical formulations and biological fluids have been reported in the literature, which include spectrophotometric procedures (Ayad et al., 2007; El-Din et al., 2006; Sultan, 2002), HPLC procedures (Fernandez et al., 2003; Bangaru et al., 2000; Xu et al., 2001) and enzyme immunosorbent assay procedures (Svensson et al., 1997).

4.1.2 Pharmacokinetics
Pharmacokinetic properties of acyclovir are listed in Table 4.1
Table 4.1: Pharmacokinetic properties of acyclovir

<table>
<thead>
<tr>
<th>S. No.</th>
<th>Parameter</th>
<th>Acyclovir</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Oral bioavailability (%)</td>
<td>15 to 30%</td>
</tr>
<tr>
<td>2</td>
<td>Urinary excretion (%)</td>
<td>Less than 15% as metabolites, remaining as parent drug</td>
</tr>
<tr>
<td>3</td>
<td>Bound in plasma (%)</td>
<td>9 to 33%</td>
</tr>
<tr>
<td>4</td>
<td>Clearance (ml/min/kg)</td>
<td>3.8 to 4.9</td>
</tr>
<tr>
<td>5</td>
<td>Half-life (h)</td>
<td>2.5 to 3.3</td>
</tr>
<tr>
<td>6</td>
<td>Steady state peak concentrations (μg/ml)</td>
<td>0.83 μg/ml for 200 mg multiple dose</td>
</tr>
</tbody>
</table>

### 4.1.3 Pharmacology

Acyclovir is a synthetic purine nucleoside analogue with *in vitro* and *in vivo* inhibitory activity against HSV 1 & HSV 2 and varicella zoster virus (VZV). The inhibitory activity of acyclovir is highly selective due to its affinity for the enzyme thymidine kinase (TK) encoded by HSV and VZV. This viral enzyme converts acyclovir into acyclovir monophosphate, a nucleoside analogue. The monophosphate is further converted into triphosphate by a number of cellular enzymes. *In vitro*, acyclovir triphosphate stops replication of herpes viral DNA.

This is accomplished in 3 ways:

1. Competitive inhibition of viral DNA polymerases
2. Incorporation into and termination of the viral DNA chain
3. Inactivation of the viral DNA polymerases. The greater antiviral activity of acyclovir against HSV compared to VZV is due to its more efficient phosphorylation by the viral TK (PDR, 2005).

#### 4.1.3.1 Drug resistance

Resistance of HSV and VZV to acyclovir can result from qualitative and quantitative changes in the viral TK and/or DNA polymerases. Clinical isolates of HSV and VZV with reduced susceptibility to acyclovir have been recovered from immune compromised patients, especially with advanced HIV infection. TK negative mutants may cause severe diseases in infants and immune compromised adults.

#### 4.1.3.2 Adverse effects

Acyclovir is generally well tolerated. When administered intravenously as acyclovir sodium it may cause local reactions at the injection site with inflammation.
and phlebitis; these reactions may be associated with extravasation that leads rarely to ulceration.

Renal impairment may occur in a few patients, it is usually reversible and is reported to respond to hydration and/or dosage reduction or withdrawal, but may progress to acute renal failure. Hepatobiliary adverse events like Hepatitis, hyperbilirubinemia, jaundice and urogenital adverse events like elevated blood urea nitrogen, elevated creatinine, hematuria, also been reported in some of the patients.

Adverse events related to skin like alopecia, erythema multiforme, photosensitive rash, pruritus, rash, Stevens-Johnson syndrome, toxic epidermal necrolysis, and urticaria have been reported in some of the patients.

Occasional adverse effects following systemic administration include increased serum bilirubin and liver enzymes, haematological changes like anemia, leukocytoclastic vasculitis, leukopenia, lymphadenopathy, thrombocytopenia, skin rashes, fever, headache, dizziness, anaphylaxis, angioedema, pain, peripheral edema, gastrointestinal distress and nausea, vomiting and diarrhoea.

Neurological effects including lethargy, somnolence, confusion, hallucinations, agitation, tremors, psychosis, convulsions and coma have been reported in a small number of patients, particularly in those receiving intravenous acyclovir and with predisposing factors such as renal dysfunction. Accelerated diffuse hair loss has also been reported.

There has also been a report of inhibition of human peripheral blood lymphocytes in samples taken from healthy subjects given acyclovir.

Adverse events like aggressive behavior, agitation, ataxia, coma, confusion, decreased consciousness, delirium, dizziness, dysarthria, encephalopathy, hallucinations, paresthesia, psychosis, seizure, somnolence and tremors have been reported particularly in older adults or in patients with renal impairment.

Table 4.2 is the compilation of various adverse events occurred during clinical trials involving acyclovir (Zovirax®, 2005)
Table 4.2: List of adverse events of acyclovir observed during clinical practice

<table>
<thead>
<tr>
<th>Condition</th>
<th>Treatment type</th>
<th>Adverse event</th>
<th>Incidence (%)</th>
<th>Active</th>
<th>Placebo</th>
</tr>
</thead>
<tbody>
<tr>
<td>Herpes simplex</td>
<td>Short-term</td>
<td>Nausea and/or vomiting</td>
<td>2.7</td>
<td>0.7</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Long-term</td>
<td>Nausea</td>
<td>4.8</td>
<td>2.4</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>Diarrhea</td>
<td>2.4</td>
<td>2.7</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>Headache</td>
<td></td>
<td>-</td>
<td>2.2</td>
</tr>
<tr>
<td>Herpes zoster</td>
<td>-</td>
<td>Malaise</td>
<td>11.5</td>
<td>11.1</td>
<td></td>
</tr>
<tr>
<td>Chicken pox</td>
<td>-</td>
<td>Diarrhea</td>
<td>3.2</td>
<td>2.2</td>
<td></td>
</tr>
</tbody>
</table>

4.1.3.3 Precautions

Acyclovir should be administered with caution to patients with renal impairment and doses should be adjusted according to creatinine clearance. Parenteral administration should be by slow intravenous infusion over one hour to avoid precipitation of acyclovir in the kidney; rapid or bolus injection should be avoided and adequate hydration maintained. The risk of renal impairment is increased by the concomitant use of other nephrotoxic drugs. Intravenous acyclovir should also be used with caution in patients with underlying neurological abnormalities with significant hypoxia or with serious hepatic or electrolyte abnormalities.

4.1.3.4 Interactions

Probenecid is reported to block the renal clearance of acyclovir. The risk of renal impairment is increased by the concomitant use of other nephrotoxic drugs.

4.1.4 Pharmaceutics

Acyclovir is available from several manufacturers. Preparations containing acyclovir are available for oral, topical and ophthalmic administration and acyclovir sodium for injectable formulation. The details are summarized in Table 4.3.

Acyclovir is available as 200, 400 and 800 mg tablets, a 200 mg capsule, a 200 mg / 5 ml suspension, a 500 or 1000 mg lyophilized powder for intravenous injection, a 50 mg/g (5% w/w) cream in a water-miscible base, a 3% (30 mg/g) ophthalmic ointment in petrolatum and a 5% (50 mg/g) ointment in a polyethylene glycol or soft paraffin base.
Table 4.3: Market status of different dosage forms of acyclovir

<table>
<thead>
<tr>
<th>Dosage form</th>
<th>API</th>
<th>Strength</th>
<th>Brand name</th>
<th>Date of approval</th>
<th>Company</th>
</tr>
</thead>
<tbody>
<tr>
<td>Capsules</td>
<td>Acyclovir</td>
<td>200 mg</td>
<td></td>
<td>25 Jan, 1985</td>
<td>GSK</td>
</tr>
<tr>
<td></td>
<td></td>
<td>400 &amp; 800 mg</td>
<td></td>
<td>30 Apr, 1991</td>
<td></td>
</tr>
<tr>
<td>Tablets</td>
<td>Acyclovir</td>
<td>5%</td>
<td>Zovirax</td>
<td>30 Dec, 2002</td>
<td>GSK</td>
</tr>
<tr>
<td>Topical cream</td>
<td>Acyclovir</td>
<td>5%</td>
<td></td>
<td>29 May, 1982</td>
<td></td>
</tr>
<tr>
<td>Topical ointment</td>
<td>Acyclovir</td>
<td>5%</td>
<td></td>
<td>22 Dec, 1989</td>
<td></td>
</tr>
<tr>
<td>Suspension</td>
<td>Acyclovir sodium</td>
<td>200 mg/m</td>
<td></td>
<td>22 Oct, 1982</td>
<td></td>
</tr>
<tr>
<td>Injection</td>
<td>Acyclovir sodium</td>
<td>Eq. 500 mg &amp;</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>1 gm base/vial</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

4.1.5 Therapeutic uses

Acyclovir and its sodium salt are active against herpes simplex viruses (HSV-1 and HSV-2), varicella-zoster infections and Epstein-Barr virus.

Acyclovir is used intravenously in the treatment of severe initial and recurrent mucocutaneous infections caused by HSV-1, HSV-2 and varicella-zoster virus (chickenpox virus) in adults and children. It is also the drug of choice for treatment of herpes simplex encephalitis. Acyclovir is frequently given orally in the management of first and recurrent episodes of mucocutaneous herpes in selected patients, for the acute treatment of herpes zoster (shingles) and for the treatment of chickenpox in adults and children. Acyclovir is also used topically in the treatment of mucocutaneous HSV infections, although it is substantially less effective than systemic therapy.

4.1.5.1 Dose

The oral doses of acyclovir for adults range from 200 mg every 4 h (while awake) to 800 mg three times a day for 5–10 days. For chronic suppression of recurrent infections, the dose is 400 mg twice a day. The oral dose for treatment of chickenpox and herpes zoster is 800 mg acyclovir every 4 h for 5–10 days. Topical treatment of the affected skin or mucous membrane (not conjunctival) with 5% ointment or cream is given up to every 3 h. For ocular herpes simplex keratitis, a 3% ointment may be applied five times daily up to every 4 h until 3 days after healing (Gennaro, 1995). In young children, acyclovir is given intravenously at 250–500 mg/m² of body surface area every 8 h. In older children and adults, intravenous injections are given at a dose of.
5–10 mg/kg every 8 h. Doses of acyclovir should be reduced in patients with renal impairment.

Patients with Acute or Chronic Renal Impairment: In patients with renal impairment, the Dose of ZOVIRAX Capsules, Tablets, or Suspension should be modified.

4.2 Excipient Profile

In addition to the drug substance, most of the pharmaceutical dosage forms contain various excipients (inactive ingredients) that could aid formulation, manufacture and subsequent administration to the patients. Performance of the dosage forms is highly dependent on the type, nature and grades of the excipients used, their concentrations and their interaction with the drug substance and also with each other. The choice of excipients and quantities should not only fulfil the formulation and manufacturability, but also enable the drug substance achieve its pharmacokinetic and therapeutic objectives. Different categories of excipients, viz. controlled release polymer, diluent, wicking agent, alkalizing/acidifying agent, lubricant, binder and glidant have been used. In this section, summary of important properties of these excipients is provided.

4.2.1 Hypromellose

Hypromellose, also called as hydroxyl propyl methyl cellulose is a water soluble polymer derived from cellulose, the most abundant polymer in nature. It is a semisynthetic polymer prepared by reacting cellulose with methyl chloride and propylene oxide (Dow, 2002a). Hypromellose is available in various grades that vary in the ratio or hydroxypropyl and methyl substitution, a factor that influences organic solubility and thermal gelation temperature or aqueous solutions. Chemical structure and commercial grades of hypromellose are shown in Figure 4.2 and Figure 4.3, respectively.
Figure 4.2: Chemical structure of hypromellose (Dow, 2002a)

Figure 4.3: Commercial grades of hypromellose from Dow Chemical Company (Dow, 2002a).

Hypromellose is an odorless and tasteless, white or creamy-white fibrous or granular powder. Soluble in cold water, forming a viscous colloidal solution; practically insoluble in hot water, chloroform, ethanol (95%), and ether, but soluble in mixtures of ethanol and dichloromethane, mixtures of methanol and dichloromethane, and mixtures of water and alcohol. Certain grades of hypromellose are soluble in aqueous acetone solutions, mixtures of dichloromethane and propan-2-ol, and other organic solvents. Some grades are swellable in ethanol (Rowe et al., 2006a).

Hypromellose is one of the widely used pharmaceutical excipient in oral, ophthalmic, nasal, and topical dosage forms. In oral formulations, it is mainly used as binder, controlled release polymer, film former in film coating compositions and thickening agent. Low viscosity grades are used as binder and film former, whereas high viscosity grades are used as release controlling excipient.

Official monograph of hypromellose is available in British pharmacopoeia, Japanese pharmacopoeia, European pharmacopoeia and United State Pharmacopeia.
4.2.2 Polyethylene oxide

Polyethylene oxide is a non-ionic and synthetic water soluble polymer available in various grades of molecular weights and viscosities. Polyethylene oxide appears as white, granular powders possess a slightly ammoniacal odor. Polyethylene oxide is soluble in water and a number of common organic solvents such as acetonitrile, chloroform, and methylene chloride. It is insoluble in aliphatic hydrocarbons, ethylene glycol, and most alcohols. Its chemical structure is shown in Figure 4.4.

Figure 4.4: Chemical structure of polyethylene oxide

Polyethylene oxide is widely used as tablet binder, controlled release polymer, thickening agent and mucoadhesive polymer (Rowe et al., 2006b). Polyethylene oxide is a non-ionic polymer and its viscosity and gelling behavior is independent of the pH. Polyethylene oxide offers a number of important properties for mucoadhesion – water solubility, hydrophilicity, high molecular weight, hydrogen bonding functionality, and good biocompatibility. These resins have a long linear chain structure which allows them to form a strong interpenetrating network with mucus. Data indicate that molecular weights of 4,000,000 and higher have the highest level of adhesion (Dow, 2000b). Polyethylene oxide is official in United States Pharmacopeia / National Formulary.

4.2.3 Carbomer

Carbomer polymers, commercially known as carbopol are high molecular weight polymers of acrylic acid. They are synthetic high-molecular-weight polymers of acrylic acid that are cross-linked with either allyl sucrose or allyl ethers of pentaerythritol. The molecular weight of carbomer resins is theoretically estimated at $7 \times 10^5$ to $4 \times 10^9$. Carbopols are white-colored, fluffy, hygroscopic powders with a slight characteristic odour. Carbomers do not dissolve but merely swell to a remarkable extent, since they are three-dimensionally cross-linked microgels (Rowe et al., 2006c). Chemical structure of carbomer is shown in Figure 4.5.
Chapter 4.0 – Drug and Excipients Profile

Figure 4.5: Chemical structure of carbomer (Rowe et al., 2006c)

In pharmaceutical preparations carbomers are used as bioadhesive agent, emulsifying agent, controlled release polymer, suspending agent, tablet binder and viscosity-increasing agent. Carbomers are anionic in nature and swell up to 1,000 times their original volume in water to form a gel when exposed to a pH environment above their pKa of 6 ± 0.5. At lower pH values the polymer is not fully swollen and the drug is released faster. As the pH increases, swelling of the polymer is greater resulting in rapid formation of the gel layer which prolongs drug release. The pH effect on the polymer is not said to impact drug release significantly in various pH media. The most significant factor impacting drug release is API solubility and how it is affected by pH (Lubrizol, 2011).


4.2.4 Povidone

Povidone occurs as a fine, white to creamy-white colored, odorless or almost odorless, hygroscopic powder. It is a synthetic excipient available in different grades depending on molecular weight. Chemical structure of povidone is shown in Figure 4.6.

Figure 4.6: Chemical structure of Povidone (Rowe et al., 2006d)

Povidone occurs as a fine, white to creamy-white colored, odorless or almost odorless, hygroscopic powder. It is freely soluble in acids, chloroform, ethanol (95%),
ketones, methanol, and water; practically insoluble in ether, hydrocarbons, and mineral oil. Povidone is mainly used as binder in oral solid dosage forms. It is also used as solubilizer in oral and parenteral dosage forms. Povidone is additionally used as a suspending, stabilizing, or viscosity-increasing agent in a number of topical, oral suspensions and solution (Rowe et al., 2006d). Official monograph of povidone is available in British Pharmacopoeia, Japanese pharmacopoeia, European Pharmacopoeia and United States Pharmacopeia.

4.2.5 **Microcrystalline cellulose**

Microcrystalline cellulose is a purified and partially depolymerized cellulose that occurs as a white, odorless, tasteless, crystalline powder composed of porous particles. It is commercially available in different grades varying in bulk density, particle size and moisture content, suitable for different processes like wet granulation, dry granulation and direct compression. Microcrystalline cellulose is primarily used as diluent and binder in oral tablet and capsule dosage forms. It is also used as adsorbent, suspending agent and tablet disintegrant (Rowe et al., 2006e). Official monograph of microcrystalline cellulose is available in British Pharmacopoeia, Japanese pharmacopoeia, European Pharmacopoeia and United States Pharmacopeia / National Formulary.

4.2.6 **Colloidal silicon dioxide**

Colloidal silicon dioxide is submicroscopic fumed silica with a particle size of about 15 nm. It is a light, loose, bluish-white-colored, odorless, tasteless, amorphous powder. Practically insoluble in organic solvents, water, and acids, except hydrofluoric acid; soluble in hot solutions of alkali hydroxide. Forms a colloidal dispersion with water. In pharmaceutical dosage forms colloidal silicon dioxide is used as adsorbent, anticaking agent, emulsion stabilizer, glidant, suspending agent, tablet disintegrant, thermal stabilizer and viscosity-increasing agent (Rowe et al., 2006f). Official monograph of colloidal silicon dioxide is available in British Pharmacopoeia, Japanese pharmacopoeia, European Pharmacopoeia and United States Pharmacopeia / National Formulary.

4.2.7 **Sodium bicarbonate**

Sodium bicarbonate occurs as an odorless, white, crystalline powder with a saline, slightly alkaline taste. The crystal structure is monoclinic prisms. Grades with
different particle sizes, from a fine powder to free-flowing uniform granules, are commercially available. It is practically insoluble in ethanol (95%) and ether and soluble 1 in 11 parts in water at 20°C. Sodium bicarbonate is generally used in pharmaceutical formulations as a source of carbon dioxide in effervescent tablets and granules. It is also widely used to produce or maintain an alkaline pH. The pH for a freshly prepared 0.1M aqueous solution at 25°C is 8.3; alkalinity increases on standing, agitation, or heating (Rowe et al., 2006g). Official monograph of colloidal silicon dioxide is available in British Pharmacopoeia, Japanese pharmacopoeia, European Pharmacopoeia and United States Pharmacopeia.

4.2.8 Magnesium stearate

Magnesium stearate as a compound of magnesium with a mixture of solid organic acids that consists chiefly of variable proportions of magnesium stearate and magnesium palmitate obtained from sources of vegetable or animal origin. Magnesium stearate is a very fine, light white, precipitated or milled, impalpable powder of low bulk density, having a faint odor of stearic acid and a characteristic taste. The powder is greasy to the touch and readily adheres to the skin. It is primarily used as a lubricant in capsule and tablet manufacture at concentrations between 0.25% and 5.0% w/w. It is also used in barrier creams (Rowe et al., 2006h). Official monograph of magnesium stearate is available in British Pharmacopoeia, Japanese pharmacopoeia, European Pharmacopoeia and United States Pharmacopeia / National Formulary.

4.2.9 Sodium alginate

Sodium alginate consists chiefly of the sodium salt of agonic acid, which is a mixture of polyatomic acids composed of residues of D-mannuronic acid and L-guluronic acid. Sodium alginate occurs as an odorless and tasteless, white to pale yellowish-brown colored powder. It is practically insoluble in ethanol (95%), ether, chloroform, and ethanol/water mixtures in which the ethanol content is greater than 30%. Also, practically insoluble in other organic solvents and aqueous acidic solutions in which the pH is less than 3 (Rowe et al., 2006i). It is slowly soluble in water, forming a viscous colloidal solution. Chemical structure of sodium alginate is shown in Figure 4.7.
Figure 4.7: Chemical structure of sodium alginate (FMC, 2008).

It is used as suspending agent, tablet and capsule disintegrant, controlled release polymer, tablet binder and viscosity increasing agent. Official monograph of sodium alginate is available in British Pharmacopoeia, European Pharmacopoeia and United States Pharmacopeia / National Formulary.

4.2.10 Citric Acid

Citric acid monohydrate occurs as colorless or translucent crystals, or as a white crystalline, efflorescent powder. It is odorless and has a strong acidic taste. The crystal structure is orthorhombic. Citric acid monohydrate occurs as colorless or translucent crystals, or as a white crystalline, efflorescent powder. It is odorless and has a strong acidic taste. The crystal structure is orthorhombic. Citric acid (as either the monohydrate or anhydrous material) is widely used in pharmaceutical formulations and food products, primarily to adjust the pH of solutions (Rowe et al., 2006j). Official monograph of citric acid is available in British Pharmacopoeia, European Pharmacopoeia and United States Pharmacopeia.

4.2.11 Mannitol

Mannitol is a hexahydric alcohol related to mannose and is isomeric with sorbitol. Mannitol occurs as a white, odorless, crystalline powder, or free flowing granules. It has a sweet taste, approximately as sweet as glucose and half as sweet as sucrose, and imparts a cooling sensation in the mouth. Microscopically, it appears as orthorhombic needles when crystallized from alcohol. Mannitol shows polymorphism. Mannitol is used as diluent in tablet and capsule dosage forms. It is used as carrier in
lyophilized preparations. It is also used as plasticizer in soft-gelatin capsules (Rowe et al., 2006k). Official monograph of citric acid is available in British Pharmacopoeia, European Pharmacopoeia and United States Pharmacopeia.

4.2.12 Sodium Starch Glycolate

Sodium starch glycolate is the sodium salt of a carboxymethyl ether of starch, containing 2.8–4.2% sodium. The molecular weight is typically $5 \times 10^5 - 1 \times 10^6$. Sodium starch glycolate is a white to off-white, odorless, tasteless, free-flowing powder. It is practically insoluble in methylene chloride and a translucent suspension in water. It is widely used as a disintegrant in tablet and capsule dosage forms (Rowe et al., 2006l). Official monograph of citric acid is available in British Pharmacopoeia and United States Pharmacopeia / National Formulary.

All the excipients used in this study are approved by The United States Food and Drug Administration (USFDA) and various other regulatory agencies across the world. Pharmacopoeial grades and trade names of the excipients used are summarized in Table 4.4

Table 4.4: Pharmacopoeial grades and trade names of excipients used in gastroretentive formulations of acyclovir.

<table>
<thead>
<tr>
<th>Excipient</th>
<th>Pharmacopoeial grade</th>
<th>Trade name</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hypromellose</td>
<td>USP</td>
<td>Methocel K100 MCR, K100 LVCR, K4 MCR, K15 MCR</td>
</tr>
<tr>
<td>Polyethylene oxide</td>
<td>USP/NF</td>
<td>Polyox WSR 303</td>
</tr>
<tr>
<td>Carborner</td>
<td>USP/NF</td>
<td>Carbopol 974P</td>
</tr>
<tr>
<td>Povidone</td>
<td>USP</td>
<td>Plasdone K 29 / 32</td>
</tr>
<tr>
<td>Microcrystalline cellulose</td>
<td>USP/NF</td>
<td>Avicel PH 101 Avicel PH 102</td>
</tr>
<tr>
<td>Colloidal silicon dioxide</td>
<td>USP/NF</td>
<td>Aerosil 200 Pharma</td>
</tr>
<tr>
<td>Sodium bicarbonate</td>
<td>USP</td>
<td>---</td>
</tr>
<tr>
<td>Magnesium stearate</td>
<td>USP/NF</td>
<td>Hyqual, vegetable source</td>
</tr>
<tr>
<td>Sodium alginate</td>
<td>USP/NF</td>
<td>Keltone HVCR</td>
</tr>
<tr>
<td>Citric acid</td>
<td>USP</td>
<td>---</td>
</tr>
<tr>
<td>Mannitol</td>
<td>USP</td>
<td>Pearlitol SD 200</td>
</tr>
<tr>
<td>Sodium starch glycolate</td>
<td>USP/NF</td>
<td>Primojel</td>
</tr>
</tbody>
</table>

USP-United States Pharmacopeia; USP/NF-United States Pharmacopeia/National Formulary