REVIEW OF LITERATURE
A virus is a small infectious agent that depends on host cells that they infect to reproduce. It is minimally constructed of two components, a genome consisting of either ribonucleic acid (RNA) or deoxyribonucleic acid (DNA) and a protein coat also called as capsid which protects the genome (Harvey and Champe, 1994). Some viruses have additional lipid membrane which covers the capsid without which they are known as naked viruses. Viruses are unique that they have been classified as both living and nonliving entities. When they are present outside of host cells, they are metabolically inert and cannot grow or multiply on their own. But, on coming in contact with a host cell, a virus can insert its genetic material into its host and take over the host's functions. There are numerous ways by which viruses can gain access to human body like eating food contaminated with virus, drinking or swimming in water, and even while breathing. Then they are able to attach themselves to the specific receptor present on cell surface, and subsequently inject their own RNA or DNA into the cell and take over the control. The cell infected with virus then produces more viral proteins and genetic material instead of its own products. Some viruses may remain dormant inside host cells for long periods, causing no obvious change in their host cells (a stage known as the lysogenic phase). But when a dormant virus is stimulated, it enters the lytic phase: new viruses are formed, self-assemble, and burst out of the host cell, killing the cell and going on to infect other cells which result in occurrence of various symptoms and finally becomes the cause of diseases (Emilani, 1993). They may lead to mild to severe illnesses in humans, animals and plants. Although there are a lot of bacteria and viruses in the world, the vast majority of them are not harmful and in fact a lot of them are very helpful. A well-known example is E. coli, which is present in the intestine and helps in digestion in addition to producing Vitamin B-complex and vitamin K (Bentley and Meganathan, 1982). In a typical life cycle of a basic virus, the virus particle first attaches to a host cell through receptors present on the cell surface. This is followed by release of viral DNA or RNA takes control over the host cell machinery. The host cell now starts making viral DNA or RNA and other viral proteins. Different viral products assemble together to form new viruses and then break free of the host cell to search for a new host cell. Sometimes, the host cell is destroyed when the new virus breaks out of the host cell, causing disease to the host. Typical life cycle of HIV is shown in Figure
2.1. Various types of diseases caused by different types of viruses are listed in the Table 2.1.

Figure 2.1: HIV replication cycle (NIAID, 2012).
Table 2.1: Diseases caused by various viruses

<table>
<thead>
<tr>
<th>Disease</th>
<th>Virus</th>
<th>Family</th>
<th>Symptoms</th>
<th>Therapy</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mumps</td>
<td>Rubulavirus</td>
<td>Paramyxoviridae</td>
<td>Swelling of salivary glands, meningitis</td>
<td>MMR (Measles, mumps and rubella) vaccination</td>
</tr>
<tr>
<td>Influenza</td>
<td>Orthomyxoviruses</td>
<td>Orthomyxoviridae</td>
<td>Chills, fever, headache</td>
<td>Antiviral drugs</td>
</tr>
<tr>
<td>Measles</td>
<td>Morbillivirus</td>
<td>Paramyxoviridae</td>
<td>Cold, rash, koplak spot formed</td>
<td>MMR vaccination</td>
</tr>
<tr>
<td>Genital Herpes</td>
<td>HSV2</td>
<td>Herpesviridae</td>
<td>Fever, genital sores</td>
<td>Not curable, acyclovir reduces healing time</td>
</tr>
<tr>
<td>Small Pox</td>
<td>Variola</td>
<td>Poxviridae</td>
<td>fever, prostration, rash, hypotension, and septic shock</td>
<td>Not curable</td>
</tr>
<tr>
<td>Rubella (German</td>
<td>Rubella sRNA virus</td>
<td>Togaviridae</td>
<td>Dangerous for pregnant resulting in premature delivery or fetal death, rash in children</td>
<td>No treatment, MMR vaccination</td>
</tr>
<tr>
<td>Measles</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Chicken Pox</td>
<td>Varicella Zoster</td>
<td>Herpesviridae</td>
<td>Respiratory system</td>
<td>Prevented vaccine or treated with acyclovir</td>
</tr>
<tr>
<td>Hepatitis A</td>
<td>Hepatitis A</td>
<td>Picornaviridae</td>
<td>liver disorders</td>
<td>Killed vaccine Havrix</td>
</tr>
<tr>
<td>Serum Hepatitis</td>
<td>Hepatitis B</td>
<td></td>
<td>Fever, weight loss, liver cirrhosis</td>
<td>Immunotherapy, vaccination for preventive measures</td>
</tr>
<tr>
<td>Hepatitis C</td>
<td>Hepatitis C virus</td>
<td>Flaviviridae</td>
<td>Liver cirrhosis, liver cancer</td>
<td>Interferon treatment</td>
</tr>
<tr>
<td>AIDS</td>
<td>Human immunodeficiency</td>
<td>Retroviridae</td>
<td>Mild fever, weight loss, Kaposi’s sarcoma, dementia,</td>
<td>Antiviral agents like inhibitors of HIV reverse transcriptase (RT), inhibitors of HIV protease and proper protection</td>
</tr>
<tr>
<td>Rabies</td>
<td>Negative strand RNA</td>
<td>Rhabdoviridae</td>
<td>Virus Multiplies in connective tissue, central nervous system leads to death.</td>
<td>Annual pre-exposure vaccination of animals and post exposure vaccination to humans.</td>
</tr>
<tr>
<td>Poliomyelitis</td>
<td>Poliovirus</td>
<td>Picornaviridae</td>
<td>Throat infection, in chronic stage paralysis results</td>
<td>Salk and Sabin vaccine</td>
</tr>
</tbody>
</table>
2.1 Human Herpes Virus (HHV)

Herpes viruses are one of the most common causative agents behind the viral infections occurring in human beings. Members of the HHV family (herpetoviridae) include: herpes simplex virus type 1 (HSV-1), herpes virus simplex type 2 (HSV-2), varicella zoster virus (VZV), Epstein-Barr virus (EBV), cytomegalovirus (CMV) and HHV-6, HHV-7, HHV-8. Herpes simplex virus (HSV) affects more than one third of the world’s population (Whitley et al., 1998) and is responsible for a wide array of human diseases, with effects ranging from discomfort to death. Herpes simplex viruses (HSV) are part of the alphaherpesviruses subfamily of herpes viruses.

These viruses fall into three categories: alpha herpes viruses (HSV-1, HSV-2, and varicella-zoster virus), beta herpes viruses (cytomegalovirus, HHV-6, and HHV-7), and gamma herpes viruses (Epstein-Barr virus, lymphocryptovirus, and HHV-8) (Carter and Saunders, 2007).

2.1.1 Human herpes virus 1

Human Herpes virus 1 (HHV-1), usually described as herpes simplex virus type 1 (HSV-1) is a very common virus, which is also known as fever blister. It is mainly the cause of cold sores around the mouth (Herpes Labialis) (Medicine Net, 2013). It also causes HSV conjunctivitis, neonatal infections and ocular lesions. At the age of 20, most Americans are infected by HSV-1. The virus lies latent in the neurons after the first episode until something sets the virus off into another eruption. Cold, flu and even stress can cause an outbreak of cold sores. The first symptoms usually appear within one or two weeks after contact with the carrier. The lesions of herpes labialis usually last for seven to 10 days then begin to resolve. HSV-1 infections are contagious and it is spread through skin to skin contact with carrier and mainly spread through sharing of shaving blades, soaps, towels, food or utensils with the person having active lesion in skin or mucous membrane.

2.1.2 Human herpes virus 2

Human herpes virus 2 (HHV-2), usually described as herpes simplex virus type 2 (HSV-2) is the cause of genital herpes (Herpes genitalis) (Hill, 2012). Indian men are more likely to be infected with HSV-2 than women, and increasing seroprevalence of this virus is associated with an increasing age (Kaur et al., 2005).
Like HSV-1, the HSV-2 infection is contagious and is spread by skin-to-skin contact. It is transmitted sexually either by oral sex or sexual intercourse. However, it can also cause cold sores in the facial area. Primary symptoms include flu, fever and mild sores. There is no documented evidence exist till date of the cause of genital herpes from the lifeless objects like towels, toilet seats etc.

2.1.3 Human herpes virus 3

HHV-3 (Varicella zoster virus, VZV) is called as either herpes varicella (the primary infection that causes chickenpox) or herpes zoster (the reactivation of the virus that causes shingles) (Hill, 2012). Chickenpox is usually a childhood disease. Over 90% of cases occur in children aged 14 years or younger. Chickenpox is acquired by direct contact with infected blister fluid or by inhalation of respiratory droplets. A person who has never been exposed to chickenpox inhales these droplets and the virus enters the lungs, and then is carried through the bloodstream to the skin where it causes a rash. Shingles occurs when dormant VZV from an initial bout of chickenpox becomes reactivated. A thin-walled, clear vesicle (a blister that looks like a dew drop) develops on top of the area of redness. This virus may also recur along nerve fiber pathways, causing multiple sores where nerve fibers end on skin cells. In shingles, entire group of nerve cells is affected so it is severe than herpes simplex. The lesions generally appear in a band-like or belt-like pattern occurring on one side of the body and are often accompanied by itching, tingling, or even severe pain. Vaccine is now available that may prevent shingles or lessen its effects (Zostavax®, marketed by Merck) (USFDA, 2013). Postherpetic neuralgia (PHN) is a complication of shingles, where the pain associated with the infection can persist for months and even years. The greater the age when the virus reactivates, the greater the chance the individual will develop PHN.

2.1.4 Human herpes virus 4

Human herpes virus 4 (HHV-4) is also known as the Epstein-Barr virus (EBV). It is the major cause of infectious mononucleosis, also known as “kissing disease”. The symptoms include a sore throat that lasts two weeks or more, swollen lymph nodes (in the neck, armpits, and groin), a persistent fever, fatigue (tiredness), and malaise (a vague feeling of discomfort). It plays a role in the development of Burkitt’s lymphoma (a rare form of lymphoma or cancer of the lymph system) and
nasopharyngeal carcinoma (cancer of the nose and throat) in humans. The incubation period for the mononucleosis is usually 7 to 14 days in children and adolescents. Mononucleosis spreads by contact with moisture from the mouth and throat of a person who is infected with the virus. EBV may cause chronic fatigue syndrome, a condition of chronic tiredness and exhaustion. Mononucleosis infection symptoms may resolve in one or two months, the EBV remains dormant in cells in the throat and blood for the rest of the person’s life.

2.1.5 Human herpes virus 5

Human herpes virus 5 (HHV-5) is the official name of cytomegalovirus (CMV) (Forsgren and Klapper, 2009). It is found in body fluids including urine, saliva (spit), breast milk, blood, tears, semen, and vaginal fluids. It is commonly transmitted from an infected pregnant woman to her unborn child. CMV causes infections including retinitis (inflammation of the retina), pneumonia, colitis (inflammation of the colon), encephalitis (inflammation of the brain), mononucleosis, pneumonia, hepatitis and uveitis. It is an opportunistic virus because the virus may not even cause any symptoms in healthy people. It can be sexually transmitted, can cause problems to newborns and can cause hepatitis. CMV can be transmitted through sexual contact, breast-feeding, blood transfusions and organ transplants. CMV infection is one of the most difficult complications of AIDS. It may lead to diarrhea, severe vision problems including blindness, infections of the stomach and intestines, and even death. CMV also leads to neural tube defects (incomplete development of the brain, spinal cord, and/or their protective coverings).

2.1.6 Human herpes virus 6

Human Herpes virus 6 (HHV-6) is a recently observed agent found in the blood cells of a few patients with a variety of diseases. It causes roseola (a viral disease causing high fever and a skin rash) in young children (Leach, 2007). It leads to chronic fatigue syndrome (CFS) and multiple sclerosis (MS), a chronic (long-term) inflammatory condition of the central nervous system (CNS) resulting in changes in sensation, visual problems, muscle weakness, depression, difficulties with coordination and speech, severe fatigue, cognitive impairment, problems with balance and pain. This
infection accounts for many of the cases of convulsions associated with fever in infancy (febrile seizures).

2.1.7 **Human herpes virus 7**

Human Herpes virus 7 (HHV-7) is even more recently observed and is closely related to HHV6 and cytomegalovirus (CMV). HHV-7 is least pathogenic as compared to HHV 6 and cytomegalovirus (CMV). It causes roseola in infants and young children.

2.1.8 **Human herpes virus 8**

Human Herpes virus 8 (HHV-8) was found in the tumors called Kaposi's sarcoma (KS) (Ablashi et al., 2002). KS forms purplish tumors in the skin and other tissues of some people with AIDS. It also causes also lympho-proliferative disorders (condition of too many white blood cells produced), primary effusion lymphoma (PEL) and Multicentric Castleman's disease (MCD).

2.2 **HSV Structure**

HSV is a large double-stranded DNA virus surrounded by an envelope of lipid glycoprotein. Figure 2.2 shows the structure of HSV. It comprises of four parts: (1) an electron-dense core containing viral DNA (2) a capsid (3) an amorphous eccentric layer of proteins, designated as tegument, which surrounds the capsid and (4) an envelope. The tegument can be 20-40 nm in thickness depending on the virus species and it may be uniformly or asymmetrically distributed around the capsid. Tegument proteins are thought to be those whose function is required promptly after initiation of infection, before expression of virus genes can take place. Envelop contains the glycoproteins (gB, gC, gD, gE, gG, gH, gI, gJ, gK, gL, gM, and gN) (Campadelli-Fiume et al., 2000) which take part in the attachment of HSV to the host cell surface and are involved prominently in attachment of the virus to the host cell surface and entry of the capsid into the cytoplasm. Glycoprotein D (gD) is the main glycoprotein responsible for receptor recognition while entry into the cytoplasm requires four glycoproteins, gB, gD, gH and gL. Glycoprotein B is the primary component involved in fusion of the virus and host cell membranes. Structure of HSV is shown in Figure 2.2.
2.3 HSV ENTRY

Viral envelope glycoproteins interact with the host cell surface binding to the heparan sulfate proteoglycan which initiates the HSV-1 entry into the cell (Spear, 2004) and allow the de-enveloped capsid to be transported to the nuclear pores. The DNA is released into the nucleus at the core. Virus replicates with the phenomenon of transcription in the nucleus by rolling circle mechanism. About 10 viral glycoproteins are designed presently (gB, gC, gD, gE, gG, gH, gI, gK, gL) which brings out the immune response. Virus gets attached to the host cell surface by glycoprotein gB and gC, whereas gD is required for entry of the virus into cells. gE and gL form a rather potent Fc receptor; gE is also required for basolateral transmission of virus in polarized cells and for efficient expression of late genes. The formation of both RNA and proteins occurs in 3 periods sequentially. The first set of DNA genome products comprises of six proteins known as immediate early proteins. Five proteins regulate the reproductive cycle of the virus, and sixth one blocks antigenic peptides presentation on the infected cell surfaces. The second set of product is called as early proteins. Early proteins play the key role in the viral nucleic acid metabolism. Third set of proteins forms the capsid and tegument that play the role as the structural component of the virus and then incorporated in the nuclear membranes for the last virions envelopment. Entry of HSV into the host cell is depicted in Figure 2.3.
2.4 Pathogenesis

Pathogenesis of HSV depends on the close relation or skin to skin contact between the seronegative and seropositive individuals. There must be a contact with shed skin for infection to take place. At the site of infection virus gets replicated in large head to tail viral genomes, which are cleaved off into unit length genomes with the help of encapsid. Replication occasionally leads to complicated disease which can be life threatening. HSV latency has been established by retrograde movement to the nuclei of sensory ganglia (Stevens et al., 1975).

2.5 Primary Infection

HSV initially affects the skin and mucous membrane. It immediately takes place after the first exposure to surrogate negative individuals. The symptoms include burning sensation at the site of viral infection, loss of appetite, dysphagia and transient vesicles which are painful when rupture and ulceration in the oral cavity (Nadelman and Newcomer, 2000).

2.6 Recurrence

After the exposure to the infection, HSV antibodies form but they do not protect against reactivation of the virus. Recurrent episodes are milder than primary
infection and also of shorter duration. Recurrent intraoral herpes mainly affects the gingival part, keratinized tissue of the hard palate; rarely it affects the dorsal part of the tongue. Frequency of recurrence varies among different people (Beauman, 2005). People suffering from severe primary infections are more prone to symptomatic outbreak. Episodes of recurrences are more frequent in men.

2.7 Treatment & Available Medications

Before the 1970s, when acyclovir (Zovirax) was introduced as an antiviral drug, cutaneous HSV infection was managed with drying agents and other local care. Newer antiviral drugs against herpes virus have emerged during the past several years, but no drug can cure herpes simplex. The infection may recur after treatment has been stopped. Even during therapy, a patient can still transmit the virus to another person. Drugs can, however, reduce symptoms and improve healing times. The first antiviral medication used to treat herpes was acyclovir. Acyclovir, famciclovir and valacyclovir are approved drugs. Famciclovir (Famvir®, marketed by Novartis) and valacyclovir (Valtrex®, marketed by GlaxoSmithKline) offer effective and convenient therapeutic choices but are often more expensive than acyclovir (Emmert, 2000). Acyclovir tablets and capsules are available in generic form and therefore remains an effective and less expensive option, but they must be taken frequently throughout the day (Zovirax®, 2005). Various options available for the treatment of HSV infections are summarized in Table 2.2.

Table 2.2: List of commercial antiviral products used for the treatment of HSV infections.

<table>
<thead>
<tr>
<th>Drug</th>
<th>Brand name</th>
<th>Dosage form</th>
<th>Route of administration</th>
<th>Manufactured by</th>
</tr>
</thead>
<tbody>
<tr>
<td>Acyclovir</td>
<td>Zovirax</td>
<td>Ointment</td>
<td>Topical</td>
<td>GlaxoSmithKline</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Tablet</td>
<td>Oral</td>
<td>GlaxoSmithKline</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Capsules</td>
<td>Oral</td>
<td>GlaxoSmithKline</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Suspension</td>
<td>Oral</td>
<td>GlaxoSmithKline</td>
</tr>
<tr>
<td>Famciclovir</td>
<td>Famvir</td>
<td>Tablet</td>
<td>Oral</td>
<td>Novartis</td>
</tr>
<tr>
<td>Valacyclovir</td>
<td>Valtrex</td>
<td>Tablet</td>
<td>Oral</td>
<td>GlaxoSmithKline</td>
</tr>
<tr>
<td>Penciclovir</td>
<td>Denavir</td>
<td>Cream</td>
<td>Topical</td>
<td>Denco Asset</td>
</tr>
</tbody>
</table>
Acyclovir is a safe, extremely well-tolerated drug and its toxicity is rare (Emmert, 2000). Data from more than 35 million patients have been consistent and reassuring (Whitley and Gnann, 1992). Adverse effects are usually mild which include nausea, vomiting, rash and headache. Lethargy, tremulousness, seizures and delirium have been reported rarely in studies on renally impaired patients (Clarke et al., 1995).

### 2.8 Acyclovir

Acyclovir, chemically known as 2-amino-1,9-dihydro-9-[(2-hydroxyethoxy)methyl]-6H-purin-6-one, is a purine nucleoside analogue, known for its potent and selective antiviral activity against viruses of the herpes group. Acyclovir is a structural analog of deoxyguanosine. In addition to HSV, it has *in-vitro* activity against Varicella-Zoster Virus (VZV), Epstein-Barr Virus (EBV), and Cytomegalovirus (CMV) (Balfour, 1988). This drug has been shown to be of clinical benefit when administered topically, orally, or parenterally for the prophylaxis and treatment of certain herpes virus infections (Balfour, 1988). It is clinically indicated for the acute treatment herpes zoster, treatment of chicken pox, and genital herpes. Acyclovir is one of the treatments of choice for treatment of initial episodes and management of recurrent episodes of genital herpes (Zovirax, 2005; NGC, 2007).

Acyclovir (first known as acycloguanosine) was synthesized in the U.S.A. as part of the Burroughs Wellcome programme for the development of guanosine nucleosides resistant to phosphorylase degradation with the first observation of antiviral activity being made by Collins & Bauer in the U.K. at the Beckenham laboratories of the former Wellcome Foundation (Clercq and Field, 2006). Currently marketed oral formulations of acyclovir include immediate release capsules, tablets and suspension. It is also available as topical cream or ointment and as solution for intravenous infusion. Topical formulations are said to be less effective than oral formulations for the management of HSV (NGC, 2007). Intravenous therapy is indicated only when the patient cannot swallow or tolerate oral medication because of vomiting. Absorption of acyclovir in the gastrointestinal tract is slow, variable and incomplete (Fletcher and Bean, 1985).

In spite of its effective antiviral activity, the use of acyclovir still has biopharmaceutics and pharmacokinetic limitations. Oral bioavailability of acyclovir is low (15 to 30%) and highly variable. It also has a short elimination half-life ($t_{1/2}$) of 2.3
h. Absorption of acyclovir from the gastrointestinal tract (GIT) is slow, variable and incomplete. Acyclovir is soluble in acidic pH and predominantly absorbed from the upper GIT. In commercially available IR dosage forms, the fraction of dose absorbed is very low due to short residence time of the dosage form at the absorption site. As a result, most of the administered drug is excreted in the feces (50–60%), in an unabsorbed form. These limitations necessitate frequent administration of acyclovir up to five times a day, leading to poor patient compliance, which in turn leads to reduced therapeutic efficacy and development of resistance. The recommended dosage regimen of acyclovir for the management of genital herpes is 200 mg every four hours, five times daily for 10 days.

2.8.1 Possible reasons for poor oral bioavailability of acyclovir

2.8.1.1 Polymorphism & pseudo polymorphism

Kristl et al. (1996) prepared anhydrous forms of acyclovir and compared its intrinsic dissolution with that of hydrated form. Dissolution of the anhydrous form was slower than the hydrated form. Apart from this work, not much of the work has been published on physicochemical properties and pharmacokinetics of various polymorphic/pseudo polymorphic forms of acyclovir. This still remains as a potential research area for improving solubility, in turn its bioavailability.

2.8.1.2 Absorption mechanism

There are conflicting reports on the existence of saturable absorption process for acyclovir in the GIT. Krasny et al. (1981) suggested that the gastrointestinal absorption of acyclovir is a saturable process, based on the non-linearity in absolute bioavailability after oral administration of increasing doses of acyclovir. They investigated pharmacokinetics of acyclovir in dogs after administration of capsule and gavage. The absolute bioavailability decreased with increasing dose in both modes of administration. Absolute bioavailability was 91, 80 and 54% for 5, 20 and 50 mg/kg, respectively after capsule administration and corresponding figures were 89, 61 and 67% after gavage dosing. But no mechanistic studies were performed to conclude the hypothesis that absorption of acyclovir is a saturable process. In another study performed by Lewis and his co-workers in 1986, bioavailability of acyclovir was found to be significantly higher when the drug was administered as intraduodenal infusion or
sipped solution as compared to conventional tablets. 2 x 200 mg of conventional tablets of acyclovir were administered to healthy male volunteers under fasted condition with 200 ml of 5% dextrose solution and followed by another 100 ml of 5% dextrose solution at exactly 1 h, 2 h and 3 h intervals. As a different form, 400 mg of acyclovir in 500 ml of 5% dextrose solution was infused into the duodenum through a naso-duodenal tube at a constant rate of 2.08 ml/min over 4 h. In the third method, volunteers sipped a similar acyclovir solution over 4 h at a sipping rate of 10.4 ml every 5 min. Mean areas under the plasma concentration time curves (AUC) for tablet, intraduodenal infusion and sipped solution were, 14.7 ± 5.1; 24.6 ± 5.1 and 28.4 ± 9.5 (n = 6), µmol l⁻¹ h. AUC for infusion and sipped solution were significantly greater than that for tablets (p<0.05). These results showed that reducing the delivery rate of acyclovir to its absorption site in the gut does significantly improve the amount absorbed and based on these results the authors suggested existence of capacity limited absorption for acyclovir.

Conversely, the pharmacokinetic parameters including bioavailability were not affected significantly as compared to oral bolus administration when acyclovir was administered as gastric infusion over 4 h period in rats (Kagan and Hoffman, 2008). peak plasma concentration (C_max) values after administration of 120 mg/kg of acyclovir as oral bolus and gastric infusion were 1200 ± 109 ng/ml and 1591 ± 156 ng/ml, respectively. AUC for corresponding treatments were 464.5 ± 68.2 µg ml⁻¹ min and 616.3 ± 60.2 µg ml⁻¹ min. Though C_max and AUC increased for gastric infusion as compared to oral bolus, but the increase was not statistically significant at p<0.01. It is possible that this increase could be statistically significant at p<0.05, but such analysis was not performed by the authors. In another study, the mechanism of uptake of acyclovir in rat jejunum using in-vitro and in-situ methods was investigated (Meadows and Dressman, 1990). Uptake of acyclovir was linear in the concentration range of 0.01 to 5 mM with in-vitro intestinal ring method. While the carrier-mediated uptake of uracil was inhibited to the extent of 31% by acyclovir, uracil did not significantly influence the uptake of acyclovir. When the single-pass perfusion was performed for acyclovir over a 500 fold concentration range of 0.1 to 5 mM, there was no overall decrease of permeability seen with increase in initial perfused drug concentration. Moreover, when 0.05 mM acyclovir was co-perfused with 1 mM DNP (2,4-
dinitrophenol), the wall permeability of acyclovir did not decrease, but resulted in elevation from 0.098 ± 0.031 to 0.212 ± 0.052. All the above findings led to the suggestion that the uptake mechanism of acyclovir in the rat jejunum is predominantly via passive diffusion.

The results of Kristl and Tukker (1998) were in agreement with the above results. The authors studied the permeability of acyclovir in S-G cells (Sweetana-Grass diffusion cells) both in mucosal to serosal (m-to-s) and serosal to mucosal (s-to-m) direction, but no polarization in transport was observed leading to the suggestion that acyclovir was absorbed passively and not by active transport. But there were two observations in their study. Firstly, comparison of apparent permeability coefficient ($P_{app}$) with lipophilicity ($\log P_{n-octanol/water}$) of the tested compounds showed a decrease of permeability with increase in $\log P$ values. Secondly the study could not derive any explanatory conclusion on the higher bioavailability of deoxyacyclovir (a prodrug of acyclovir, at least 75% of the administered dose of deoxyacyclovir is absorbed) than that of acyclovir. In another study conducted by Wilson et al. (1987), delay in the gastric emptying and prolonged intestinal transit time induced by a heavy breakfast significantly decreased the absorption of acyclovir. Wilson et al. (1987) investigated the theory that reduction of the rate of gastric emptying may increase the absorption of acyclovir by two mechanisms, firstly by increasing the contact time with gastric acid and secondly by slow delivery from the stomach to the sites of absorption in the intestine. Acyclovir suspension containing anion exchange resin radiolabelled with (99mTc) pertechnetate was administered to healthy subjects immediately following heavy and light meals, and blood levels of the drug were measured over a 24 h period. Transit of the marker was followed by gamma scintigraphy. Followed by a heavy meal, gastric emptying was significantly greater and small intestinal transit time was slower as compared to lighter meal, though the latter effect was unexpected. $C_{max}$ and the AUC were significantly greater when the drug was administered with lighter meal compared to the heavy meal, in spite of higher gastric emptying time and slower small intestinal transit time followed by heavy meal. Though this study could not prove the intended theory, it has to be noted that the influence of food on drug absorption is a very complex process and involves multiple factors (Schmidt and Dalhoff, 2002).
In a recent study the regional absorption of acyclovir in a rat GIT model was investigated by Liu et al. (2010). The absorption of acyclovir in different segments of GI tract for 3 h were 9.46 ± 0.62%, 20.22 ± 1.50%, 15.7 ± 1.33%, 9.15 ± 1.01%, and 4.59 ± 0.48% from stomach, duodenum, jejunum, ileum and colon, respectively. Though these results suggest that the absorption of acyclovir is predominant from upper parts of gastrointestinal tract, the drug does get absorbed from colon to a greater extent. Hence there could be reasons other than regional absorbability that are responsible for poor bioavailability of acyclovir. In a study conducted by Merzlikine et al. (2009), acyclovir exhibited poor apical to basolateral permeability (P$_{\text{app},A\rightarrow B}$ = 2.84 ± 0.8 × 10$^{-6}$ cm/sec), which was similar to the standard probe for the paracellular absorption, mannitol (P$_{\text{app},A\rightarrow B}$ = 2.53 ± 0.18 × 10$^{-6}$ cm/sec). This observation, in addition to the increase in P$_{\text{app},A\rightarrow B}$ of acyclovir in the presence of tight junction modulators, led to the conclusion that this drug is absorbed via paracellular transport.

### 2.8.1.3 P-glycoprotein (P-gp) efflux

A characteristic feature of P-gp substrates is that they show a higher transport from the basolateral to the apical (B→A) than from the apical to the basolateral (A→B) side of an intestinal membrane. Palmberger et al. (2008) studied the transport of acyclovir from A→B (absorptive) and B→A (secretory) across rat intestine and Caco-2 cell monolayers. Permeability coefficients (P$_{\text{app}}$) were determined for acyclovir in buffer and in the presence of verapamil, a calcium channel antagonist that is known to have inhibitory effect on P-gp. The P$_{\text{app}}$ of secretory transport was 2.3 and 2.5-fold higher than absorptive transport for acyclovir in rat intestine and Caco-2 cell monolayers, respectively. In the presence of verapamil, the absorptive and secretory transport of acyclovir was not significantly different due to the P-gp inhibitory effect of verapamil. These findings provided further evidence to the earlier reports that P-gp inhibitors could improve absorption of acyclovir (Salama et al., 2004; Yang et al., 2004).

### 2.9 Approaches for Enhancement of Oral Bioavailability of Acyclovir

#### 2.9.1 Self microemulsifying drug delivery system (SMEDDS)

Patel and Sawant in (2007) prepared and optimized SMEDDS with high loading of acyclovir with an objective to improve its oral bioavailability. Comparative
bioavailability study of optimal formulation and drug solution was performed in male albino rats. As compared to the drug solution, the SMEDDS formulation exhibited 2.2-fold and 3.5-fold higher C\text{max} and AUC, respectively. There are various modes by which drug absorption is enhanced from the SMEDDS have been listed by the authors (Mehta et al., 2011), but in the case of acyclovir, following could be applicable:

- Inhibition of gastric motility due to lipid phase of emulsion, which allowed more time for drug dissolution and absorption.
- Increased mucosal permeability via incorporation of lipid from mixed micelles and enhanced mesenteric lymph flow.
- Increased dissolution due to the large surface area offered by the emulsion.

2.9.2 Niosomes

Attia et al. (2007) prepared acyclovir niosomes by the conventional thin film hydration method in an attempt to improve its oral bioavailability. Niosomes contained a lipid mixture of cholesterol, span 60, and dicetyl phosphate in the molar ratio of 65:60:5, respectively. Niosomal dispersion was found to have sustained release characteristics in-vitro as compared to free drug. Pharmacokinetic study was performed in male New Zealand white rabbits. The niosomal drug dispersion showed significantly (p<0.005) higher values for C\text{max}, t\text{1/2}, AUC\text{0→∞}, and mean residence time (MRT); and significantly (p<0.005) lower values for absorption (k\text{a}) and elimination (k\text{el}) rate constants compared with free drug solution. The increase in the MRT and AUC\text{0→∞} values and the decrease in the k\text{a} value reflected the sustained release effect of the niosomal formulation and were in line with in-vitro drug release study. The sustained release effect could be due to the penetration of the drug into deeper layers of intestinal mucosa facilitated by the carrier effect of niosomes, followed by slow release of encapsulated drug. The relative bioavailability of niosomal formulation compared with drug solution was found to be 2.55±1.82. The improved bioavailability could be due to lipophilic nature of the niosomal formulation, which enhances partitioning to the mucosa, effect of the nonionic surface-active agent (span 60) on the barrier function of the GI mucosa and prolonged localization of drug-loaded niosomes at the site of absorption.
2.9.3 Beta-cyclodextrin

Rossel et al. (2000) prepared inclusion complexes of acyclovir with beta-cyclodextrin (ACY-βCD) in solid and solution state. Formation of 1:1 stoichiometric complex was investigated and confirmed by various characterization techniques such as $^1$H-NMR, X-ray diffraction, differential scanning calorimetry and thermogravimetry. Dissolution of ACY-βCD complex was much higher than the pure drug alone or its physical mixture with βCD. The increase in dissolution in the case of complex was attributed to the increased solubility due to decrease in crystallinity of the inclusion complex. Though the authors did not conduct in-vivo studies, Luengo et al. (2002) studied the pharmacokinetics of ACY-βCD complex. Acyclovir, its 1:1 inclusion complex with βCD and 50:50 mixture of pure drug and the inclusion complex were administered intra-intestinally to male Sprague-Dawley rats in doses equivalent to an acyclovir dose of 75 mg/kg. Both the ACY-βCD complex and the acyclovir/complex mixture had a higher bioavailability than acyclovir in terms of AUC. By comparing the AUC by the Friedman Test, there was no statistically significant difference between acyclovir and the complex (p>0.05). However, there were statistically significant differences between acyclovir and the acyclovir/complex mixture and between the complex and the acyclovir/complex mixture (p<0.05). Small number of animals used in this study (4 each for acyclovir and complex, and 2 for the mixture) could be responsible for such an observation. Further detailed studies would be required on the effect of acyclovir inclusion complex with βCD on bioavailability of acyclovir.

2.9.4 p-Glycoprotein inhibition

Salama et al. (2004) found that the apical to basolateral (A→B) apparent permeability coefficient ($P_{app}$) of acyclovir was significantly increased by 23% (p<0.05) when the drug was incubated with an enaminone, DM27, which is a P-gp inhibitor. This increase was obtained only with $10^{-8}$ M concentration of DM27, but not at lower or higher concentrations ($10^{-4}$, $10^{-5}$, $10^{-6}$, $10^{-7}$ & $10^{-10}$ M). Possible reasons for this observation were not discussed. Palmberger et al. (2008) also studied the effect of P-gp inhibition by novel thiolated chitosans on permeability of acyclovir. Effect of three chitosan–4-thiobutylamidine (Chito–TBA) conjugates with increasing molecular mass (Chito-9.4 kDa–TBA, Chito-150 kDa–TBA and Chito-600 kDa–TBA) on transport of
acyclovir across rate intestinal mucosa and Caco-2 cell monolayer was studied. In comparison to buffer, the transport of acyclovir in presence of 0.5% (m/v) unmodified chitosan, 0.5% (m/v) Chito-150 kDa–TBA and 0.5% (m/v) Chito-150 kDa–TBA with 0.5% (m/v) reduced glutathione (GSH), was 1.3, 1.6 and 2.1-fold improved, respectively. Transport studies across Caco-2 cell monolayers showed that P-gp inhibition is dependent on the average molecular mass of thiolated chitosan showing following rankorder: 0.5% (m/v) Chito-150 kDa–TBA/GSH > 0.5% (m/v) Chito-9.4 kDa–TBA/GSH > 0.5% (m/v) Chito-600 kDa–TBA/GSH. Tablets of acyclovir prepared from thiolated polymers showed sustained in-vitro drug release. The degree of retardation was dependent on the average molecular mass of polymer. Based on the results of permeability studies and in-vitro release characteristics Chito-150 kDa–TBA was identified to have the most appropriate polymeric chain length.

2.9.5 Microemulsions

Ghosh et al. (2006) designed a microemulsion based drug delivery system to improve poor oral bioavailability of acyclovir. Quaternary microemulsion system of water / Labrasol / Plurol Oleique / Labrafac containing 5% concentration of acyclovir was developed and optimized through a pseudo ternary phase diagram. The rate of diffusion of the drug from microemulsion was found to be faster than that from tablet in intestinal permeability studies using rat duodenum. After 5 h of diffusion the fraction of drug diffused from microemulsion was 85%, which was much higher than the fraction diffused from tablet (69%). Pharmacokinetics of the microemulsion was studied in male albino Sprague-Dawley rats in comparison with intravenous injection and tablets. Microemulsion formulation resulted in more sustained absorption of acyclovir than tablets. Time to peak plasma concentration($t_{\text{max}}$) of microemulsion formulation and tablets was 3 h and 0.5 h, respectively. $C_{\text{max}}$ and AUC of acyclovir from microemulsion were 1.9-fold and 12.8-fold higher than tablets. When compared with intravenous administration, absolute bioavailability of tablet and microemulsion were 2.2 and 27.9 %, respectively. The improvements seen with respect to microemulsions were statistically significant (p<0.01). Enhanced absorption of acyclovir from microemulsion was explained in terms of huge surface area, increase in the intestinal permeability due to the presence of surfactants and stability of the formulation in the GIT.
2.9.6 Multiple emulsions

Paul et al. (2013) developed water-in-oil-in-water type multiple emulsions (w/o/w emulsions) of acyclovir and investigated its oral bioavailability in comparison with drug solution. Multiple emulsions (ME) were prepared by using different concentrations (15 and 20%) of Span-80 and Span-83 as lipophilic surfactants and Brij-35 as hydrophilic surfactant. Optical photomicrographs confirmed multiple nature of ME and that the samples belonged to type C containing many small droplets in the internal phase of the multiple globules (Florence and Whitehill, 1982). Drug release studies through dialysis bag and rat intestine revealed initial rapid release followed by a much slower release. ME were found to be more stable in refrigerator than in room temperature. In-vivo studies of most stable ME were conducted on albino rats. ME achieved much higher C<sub>max</sub> (12.98 ± 0.98 and 14.82 ± 1.11 μg/ml for 15% Span-80 and 20% Span-83, respectively) than plain drug solution (8.05 μg/ml). ME containing 15% Span-20 showed 4.25 times and ME containing 20% Span-83 showed 4.6 times increase in the AUC than plain drug solution indicating better absorption from GI mucosa and higher bioavailability as compared to plain solution. Plasma concentrations achieved by ME were more consistent and sustained than plain drug solution.

2.9.7 Absorption enhancers

Shah et al. (2008) investigated effect of absorption enhancers, dimethyl βcyclodextrin (DMβCD), chitosan hydrochloride (CH) and sodium lauryl sulfate (SLS) on trans-epithelial permeation of acyclovir across Caco-2 and Madin-Darby canine kidney (MDCK) cell monolayers. Permeation of acyclovir was studied for the drug alone, drug with different concentrations of individual absorption enhancers and combination of absorption enhancers. P<sub>app</sub> values of acyclovir in the absence of absorption enhancers were 0.352 ± 0.07×10^{-6} cm/sec and 0.523 ± 0.011×10^{-6} cm/sec in Caco-2 and MDCK cell monolayers, respectively. These values increased significantly in presence of 1%, 3% and 5% DMβCD, 0.1%, 0.3% and 0.5% CH and 0.009%, 0.012% and 0.015% SLS (p<0.05). Similarly, increases in P<sub>app</sub> in presence of combination of absorption enhancers, 5% w/v DMβCD+0.5% w/v CH, 0.5% w/v CH+0.015% w/v SLS and 5% w/v DMβCD+0.015% w/v SLS were also significant (p<0.05). P<sub>app</sub> values of acyclovir in the presence of combination of absorption enhancers were higher than that in the presence of individual agents indicating
synergistic effect of combinations. Highest enhancement of $P_{\text{app}}$ was observed with the combination of 5% w/v DMβCD+0.5% w/v CH. This was attributed to the extraction of phospholipids from the biomembrane by DMβCD, once the tight junctions are opened upon interaction of CH.

Merzlikine et al. (2009) investigated the impact of the ability of chitosan glutamate and Carbopol 974P to modulate the tight junctions in the intestinal wall on the bioavailability of acyclovir. The authors evaluated the influence of chitosan glutamate, Carbopol 974P, alone and in combination with disodium EDTA (EDTA–Na$_2$), on the in-vitro Caco-2 permeability and oral rat pharmacokinetic profile of acyclovir. The presence of chitosan glutamate (1%) increased the apical to basolateral permeability ($P_{\text{app,A→B}}$) of acyclovir from $2.84 \pm 0.8 \times 10^{-6}$ cm/sec to $11.6 \pm 0.37 \times 10^{-6}$ cm/sec, a significant 4.1-fold increase ($p < 0.05$). The increases in $P_{\text{app,A→B}}$ observed in presence of chitosan glutamate (1%)+EDTA–Na$_2$ (0.01%) and chitosan glutamate (3%) were 4.6- and 3.4-folds, respectively, relative to control ($p<0.05$). Carbopol 974P (1%) and Carbopol 974P (1%)+ EDTA–Na$_2$(0.01%) increased $P_{\text{app,A→B}}$ by 1.2- and 1.5-folds, respectively, relative to control, but the results were not statistically significant ($p>0.05$). In rats, chitosan glutamate (1–3%) and chitosan glutamate (1%)+EDTA–Na$_2$ (0.01%) formulations led to 1.7- to 2-fold increase in AUC and absolute bioavailability of acyclovir and 1.5- to 3.1-fold increase in the renal recovery of acyclovir compared to control ($p<0.05$). These results also supported the findings of Shah et al. (2008) that modulation of tight junctions can be a viable approach to overcome the limited oral bioavailability of acyclovir.

2.9.8 Sustained release formulations

Sustained release (SR) formulations of acyclovir have been studied for two reasons. First reason is to improve patient compliance by reducing the dosing frequency of the drug. The second reason is to improve the bioavailability based on the reports that the absorption of acyclovir is a carrier mediated saturable process and slow release of drug would replenish the carriers. Yang and Hu (2006) studied the single dose pharmacokinetics of SR and IR tablets of acyclovir in dogs. Sustained release tablets resulted in much prolonged absorption. Sustained release tablets exhibited later $t_{\text{max}}$, lower $C_{\text{max}}$ and longer MRT and higher AUC as compared to IR tablets. The relative bioavailability of acyclovir SR tablets was 152% with reference to IR tablets. The
pharmacokinetic differences between sustained and immediate release tablets were statistically significant (p<0.01 for AUC and p<0.05 for other parameters). Interestingly an earlier study performed on human volunteers compared 200 mg SR tablets and 100 mg conventional tablets did not result in significant improvement in bioavailability (Zhang et al., 2001). The bioavailability of SR tablets relative to conventional tablets following single and multiple dosing was 105.9±12.0% and 95.2±8.4%, respectively. These results were not significantly different when analyzed using ANOVA and two sided t-test procedures.

Gastric mucoadhesive drug delivery systems have been widely studied to prolong the gastric residence time of drugs possessing absorption window in the upper parts of GIT. The advantage of improving bioavailability of acyclovir by prolonging gastric residence was first established in a study by Groning et al. (1998). The authors prepared a press coated magnetic depot tablet formulation containing carnauba wax coated disc shaped magnet as the inner core. The inner core was surrounded by two compression coated layers containing acyclovir along with a release controlling polymer hypromellose (Methocel K4M). The two coats contained different amounts of acyclovir and about 10% polymer. The formulation used in the pharmacokinetic study contained 160 mg and 40 mg of acyclovir per tablet in the inner layer and outer layer, respectively. In-vitro drug release of this formulation showed a sustained drug release profile over 12 h. Magnetic tablets and immediate release tablets were administered as two treatments of a three way cross-over study in five healthy male subjects. In the third treatment, an external magnet was placed at the stomach level of the subjects for 12 h in an attempt to prolong the gastric residence. The plasma concentration profiles showed that higher and longer lasting plasma concentrations can be achieved after administration of magnetic depot tablets when the external magnet is placed at stomach level as compared to the same formulation administered without the external magnet. The differences in plasma concentrations were statistically significant at 7, 8, 10 and 12 h after the ingestion of the magnetic depot tablet with an extracorporal magnet present. In three out of five subjects the AUC, which were obtained with the depot tablets, are increased after administration in presence of an extracorporal magnet. Though the AUC of acyclovir in presence of extracorporal magnet was not higher than immediate release tablets, the AUC was much lower in the absence of the magnet. This study established
the potential of gastroretention to improve bioavailability of acyclovir as compared to non-gastroretentive dosage forms.

Dhaliwal et al. (2008) developed mucoadhesive microspheres using chitosan, thiolated chitosan, Carbopol 71G and Methocel K15M as mucoadhesive polymers for gastroretentive delivery of acyclovir. Microsphere formulations containing chitosan and thiolated chitosan were prepared by emulsion-chemical crosslinking method, whereas those containing Carbopol 71G and Methocel K15M were prepared by spray drying method. The mucoadhesion time of microspheres in pig intestine followed the rank order of thiolated chitosan (8.0±0.8 h) > chitosan (3.1±0.4 h) > Carbopol 71G (1.1±0.2) > Methocel K15M (0.2±0.1 h). The highest mucoadhesion time observed with thiolated chitosan was attributed to formation of strong covalent bonds (disulfide bonds) with mucin due to the presence of thiol groups. All microsphere formulations exhibited rapid swelling and sustained in-vitro drug release as compared to plain drug. Microspheres containing thiolated chitosan had prolonged retention in the upper GIT. In the GI distribution study using 6-Carboxyfluorescein loaded thiolated chitosan microspheres, 22.3±3.1% fluorescence was recovered from stomach after 2 h. 41.6±2.9% and 26±2.1% fluorescence were recovered after 4 h and 10 h, respectively, from duodenum and jejunum portions of intestine. These were about 2-fold higher in comparison to chitosan, Carbopol 71G and Methocel K15M microsphere formulations and was attributed to the better mucoadhesive properties of thiolated chitosan at pH 5–6, the pH of duodenum and jejunum regions of intestine. All microsphere formulations were able to maintain higher plasma concentrations than drug solution, with exceptionally high levels from thiolated chitosan microspheres. It exhibited nearly four times higher AUC$_{0-24}$ of acyclovir (1091 ± 51 ng h ml$^{-1}$) as compared to drug solution (282 ± 28 ng h ml$^{-1}$). It also maintained the plasma concentration up to 24 h, but the drug solution could maintain only for 5 h.

Liu et al. (2010) evaluated in-vivo bioavailability of acyclovir from mucoadhesive microspheres in comparison with conventional tablets in beagle dogs. The mucoadhesive microspheres had sustained in-vitro drug release up to 12 h. The same was reflected as increased $t_{\text{max}}$ in-vivo from 2.33 h (conventional tablets) to 5 h (mucoadhesive microspheres). Most of the microspheres were retained in stomach even after 6 h of oral administration to rats and beagle dogs. Though the $C_{\text{max}}$ of
microspheres did not differ significantly from conventional tablets, relative bioavailability was found to be 145 %. Tao et al. (2009) prepared mucoadhesive microspheres of acyclovir using ethylcellulose as matrix former and Carbopol 974P as mucoadhesive polymer. Emulsion solvent evaporation method was used for preparation of microspheres. In-vitro drug release of the drug from microspheres was faster when the concentration of Carbopol was increased. This was attributed to the formation of hydrophilic channels on the water-insoluble ethylcellulose leading to increased diffusion of drug. The increase in Carbopol concentration also altered the release mechanism from fickian to anomalous (non-fickian) mechanism by accelerating erosion of the swelling matrix resulting in a combination of diffusion and erosion mechanism of drug release. On the other hand, increase in Carbopol concentration increased the mucoadhesion and gastric retention due to its numerous carboxyl groups which facilitate the formation of hydrogen bonds with mucus. Oral administration to rats demonstrated significant advantages of mucoadhesive microspheres (Carbopol to ethylcellulose ratio of 1:3) over suspension. Microspheres had more sustained plasma concentrations than suspension but the peak plasma concentration was slightly lower (627.2 ng/ml for microspheres vs. 750.5 ng/ml for suspension). The AUC$_{0-+}$ (6055.9 nghm$^{-1}$) and MRT (7.2 h) for microspheres were significantly higher than that of suspension (2335.6 nghm$^{-1}$ and 3.7 h, respectively) (p<0.05).

2.10 Gastroretentive Approaches

A gastroretentive drug delivery system (GRDDS) is the one which remains in the stomach for a prolonged period of time and releases the drug in the controlled manner. They are increasingly gaining importance among novel drug delivery systems because the biggest advantage associated with them is their ease of preparation in the form of tablets which are perhaps till date one of the most widely used delivery systems for both old and newly discovered drugs worldwide. It is one of the most feasible approaches for achieving a prolonged and predictable drug delivery profile in the GI tract or to control the gastric residence time. Oral controlled release (CR) / sustained release (SR) / extended release (ER) dosage forms have retained prominence for the past 3 decades due to their clinical advantages in comparison with their IR forms. However, the conventional CR formulations are not suitable for drugs possessing a narrow absorption window in the upper parts of GIT. GRDDS are basically used to
sustain the release of drug in the stomach, which is why they are unlike the conventional oral sustained release drug delivery systems. These conventional formulations are rapidly cleared from the upper GIT, resulting in the release of a significant fraction of the drug in non-absorbing distal segments of the GIT. This leads to a short absorption phase and poor bioavailability of the drug. Many drugs, such as ciprofloxacin, ofloxacin, levodopa, iron, and acyclovir, are preferentially absorbed from the upper GIT. It has been reported that, when drugs with a narrow absorption window are formulated as GRDDS, they have higher bioavailability due to an extended absorption phase (Arora et al., 2005). The ciprofloxacin once daily tablet (Cifran OD®) and ofloxacin once daily (Zanocin OD®) are the well-known commercially available GR formulations. Marketed products based on GRDDS are summarized in Table 2.3 (Pawar et al., 2011). After oral administration, GR formulations are retained within the stomach and therein release the drug in a controlled manner, so the drug is supplied continuously to its absorption sites in the upper GIT. This would be the best mode of administration for drugs with absorption window in upper parts of the GIT to achieve the pharmacokinetic and pharmacodynamic advantages of CR dosage forms.

GRDDS are advantageous for the following types of drugs:

- Drugs which are mainly absorbed in the stomach e.g. ciprofloxacin, amoxicillin, furosemide
- Drugs which are unstable in colon can be made to retain in the stomach for proper absorption
- Drugs which are effective only for local diseases of stomach e.g. antacids, misoprostol
- Weakly basic drugs which are poorly soluble in basic environment
- Drugs which have narrow absorption window

GRDDS are not suitable for following types of drugs:

- Drugs which are not stable in acidic environment cannot be formulated into these types of drug delivery systems
- Drugs which have limited solubility in the stomach are also not suitable for gastroretention
Drugs which cause gastric irritation are the least possible candidates for gastroretention.

**Table 2.3: Marketed products based on GRDDS.**

<table>
<thead>
<tr>
<th>Product</th>
<th>Remarks/type/technology</th>
<th>Active ingredient</th>
<th>Company</th>
</tr>
</thead>
<tbody>
<tr>
<td>Riomet OD</td>
<td>Effervescent floating system</td>
<td>Metformin HCl</td>
<td>Ranbaxy, India</td>
</tr>
<tr>
<td>Cifran OD</td>
<td>Effervescent floating Form</td>
<td>Ciprofloxacin</td>
<td>Ranbaxy India</td>
</tr>
<tr>
<td>Zanocin OD</td>
<td>Effervescent floating Form</td>
<td>Ofloxacin</td>
<td>Ranbaxy India</td>
</tr>
<tr>
<td>Inon Ace</td>
<td>Foam based floating system</td>
<td>Síméthicone</td>
<td>Sato Pharma, Japan</td>
</tr>
<tr>
<td>Gabapentin GR</td>
<td>Polymer-based swelling technology: AcuForm™</td>
<td>Gabapentin</td>
<td>Depomed, USA(In phase 3 clinical trial)</td>
</tr>
<tr>
<td>ProQuin XR</td>
<td>Polymer-based swelling technology: AcuForm™</td>
<td>Ciprofloxacin</td>
<td>Depomed, USA</td>
</tr>
<tr>
<td>Glumetza</td>
<td>Polymer-based swelling technology: AcuForm™</td>
<td>Metformin HCl</td>
<td>Depomed, USA</td>
</tr>
<tr>
<td>Metformin GR™</td>
<td>Polymer-based swelling technology: AcuForm™</td>
<td>Metformin HCl</td>
<td>Depomed, USA</td>
</tr>
<tr>
<td>Kadian</td>
<td>—</td>
<td>Morphine sulfate</td>
<td>Sumitomo Pharma, Japan</td>
</tr>
<tr>
<td>Prazopress XL</td>
<td>Effervescent and swelling-based floating system</td>
<td>Prazosin HCl</td>
<td>Sun Pharma, Japan</td>
</tr>
<tr>
<td>Metformin HCl LP</td>
<td>Minextab Floating®</td>
<td>Metformin HCl</td>
<td>Galenix, France</td>
</tr>
<tr>
<td>Cafeclor LP</td>
<td>Minextab Floating®</td>
<td>Cefaclor</td>
<td>Galenix, France</td>
</tr>
<tr>
<td>Tramadol LP</td>
<td>Minextab Floating®</td>
<td>Tramadol</td>
<td>Galenix, France</td>
</tr>
<tr>
<td>Cipro XR</td>
<td>Erodible matrix based system</td>
<td>Ciprofloxacin HCl</td>
<td>Bayer, USA</td>
</tr>
<tr>
<td>Baclofen GRS</td>
<td>Coated multi-layer floating &amp; swelling system</td>
<td>Baclofen</td>
<td>Sun Pharma, India</td>
</tr>
<tr>
<td>Coreg CR</td>
<td>Gastro retention with osmotic system</td>
<td>Carvedilol</td>
<td>GlaxoSmithKline</td>
</tr>
<tr>
<td>Madopar CR</td>
<td>Floating, CR capsule</td>
<td>Levodopa and Benserazide</td>
<td>Roche, UK</td>
</tr>
<tr>
<td>Liquid gaviscon</td>
<td>Effervescent floating liquid alginate preparation</td>
<td>Alginic acid and Sodium bicarbonate</td>
<td>Reckitt Benckiser Healthcare, UK</td>
</tr>
<tr>
<td>Valrelease</td>
<td>Floating capsule</td>
<td>Diazepam</td>
<td>Roche, UK</td>
</tr>
<tr>
<td>Cytotec</td>
<td>Bilayer floating capsule</td>
<td>Misoprostol (100mcg/200mcg)</td>
<td>Pharmacia Limited, UK</td>
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<tr>
<td>Topalkan</td>
<td>Floating liquid alginate</td>
<td>Aluminum magnesium antacid</td>
<td>Pierre Fabre Medicament, France</td>
</tr>
<tr>
<td>Conviron</td>
<td>Colloidal gel forming FDDS</td>
<td>Ferrous sulfate</td>
<td>Ranbaxy, India</td>
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</tbody>
</table>
2.11 Anatomy and Physiology of the GIT

To date, the design of oral drug delivery systems has largely been based upon an empirical understanding of GI anatomy and physiology. To successfully modulate the GI transit time of a drug delivery system through GRTDDS for maximum GI absorption of drugs and site-specific delivery, one needs thorough understanding of characteristics of the human GIT.

The GIT is essentially a tube about nine meters long that runs through the middle of the body from the mouth to the anus and includes the throat (pharynx), esophagus, stomach, small intestine (consisting of the duodenum, jejunum and ileum) and large intestine (consisting of the cecum, appendix, colon and rectum) (Singh et al., 2011). The wall of the GIT has the same general structure throughout most of its length from the esophagus to the anus, with some local variations for each region. The stomach is an organ with a capacity for storage and mixing. The wall of the stomach is structurally similar to other parts of the digestive tube, with the exception that the stomach has an extra oblique layer of smooth muscle inside the circular layer, which aids in performance of complex grinding motions (Nieuwanhoven et al., 1999). The main divisions of the stomach are cardia, fundus, body, pylorus and antrum, as shown in Figure 2.4.

![Figure 2.4: Pictorial representation of the anatomy of stomach](image)
2.11 GI motility

The GIT exhibit a cyclic pattern contractile activity. The GIT is in a state of continuous motility consisting of two modes: fasting contractile activity and fed contractile activity. This process is characterized by a distinct cycle of electromechanical activity known as the migrating myoelectric complex (MMC).

2.11.1 Fasting contractile activity

This series of events that cycle through the stomach and small intestine is divided into four consecutive phases (Wilson and Washington, 1989; Washington et al., 2001):

- Phase I: This is a phase when stomach and intestine have no motor activity and this phase lasts for 40 to 60 min when no food is ingested.
- Phase II: At the end of Phase I, series of mixing contractions begin both in antrum and duodenum that build up over a period of 40 to 60 min.
- Phase III: This phase lasts for 5 to 15 min characterized by circular powerful peristaltic waves, which sweep from stomach through entire small intestine up to the cecum. In this phase, indigestible solids are removed from the fasted stomach.
- Phase IV: This phase lasts for 0 – 5 min and is a transition period of decreasing activity until the next cycle begins.

At any point of time during the above four phase, if food is eaten, the GIT returns to fed state contractile activity. This whole process is depicted in Figure 2.5.
2.11.1.2 Fed contractile activity

With a meal, the cyclic recurring phase III activity of the IMMC cycle is replaced with the fed pattern of contractile activity. In the antrum the powerful contraction of phase III activity are replaced by lower-amplitude propagating contractions. Mixing and grinding are carried out by a series of peristaltic waves which originate in mid-body as a shallow indentation and gradually deepen as they progress toward the duodenum (Washington et al., 2001). The force of contractions is only 15-25% of that of phase III activity. Thus, the reduced force of antral contractions, along with the closures of the pylorus, is likely responsible for retaining non digestible solids of a critical size (1 to 3 mm) in the stomach until the digestive state is complete and fasting contractile activity returns.
2.11.2 Mucus

Mucus secreted continuously by the specialized goblet cells located throughout the GIT plays a cytoprotective role. Mucus is a translucent viscid secretion comprising mainly of glycoproteins that forms a thin, continuous gel blanket adherent to the mucosal epithelial surface (Edgar, 1992). The mean thickness of the layer varies from about 50 to 450 μm in humans. Mucus is composed of water (95%), glycoproteins and lipids (0.5-5%), mineral salts (1%) and free proteins (0.5-1%) (Voynow and Rubin, 2009). Mucus glycoproteins are high molecular weight proteins possessing covalently attached oligosaccharide units (Figure 2.6).

![Figure 2.6: Schematic representation of glycoprotein chain](image)

2.11.3 Regional variability in gastrointestinal absorption

Drugs exhibiting absorption from only a particular portion of the GIT or showing difference in absorption from various regions of the GIT are said to have regional variability in GI absorption. Such drugs show ‘absorption window’ (Chawla et al., 2003). This absorption window is observed due to following factors.
2.11.3.1 Physico-chemical factors

- pH-dependent solubility: A drug should be in the solubilized form to cross the biological membrane. Since most of the drugs are absorbed by passive diffusion of the unionized form, the extent of ionized and unionized forms at a certain pH can influence predominant absorption from a particular region of the GIT, leading to the phenomenon of ‘absorption window’.
- pH-dependent stability: pH-dependent degradation of drugs can cause variation in extent of absorption from various regions in the GIT.
- Enzymatic degradation: Degradation of the drug due to the presence of certain enzymes in a particular region of the GIT can lead to regional variability in absorption of drugs, which are substrates to that enzyme (Chungi et al., 1979).

2.11.3.2 Physiological factors

- Mechanism of absorption: drugs absorbed by active and facilitated transport mechanism show regional specificity due to the presence of these mechanisms only in a particular region of the GIT.
- Microbial degradation: drugs that are degraded by microbes are likely to show regional variability in absorption from the GIT.

2.11.3.3 Biochemical factors

Cytochromes P450 (CYP3A) is abundantly present in the intestinal epithelium. Its activity decreases longitudinally along the small intestine, with the levels rising slightly from the duodenum to the jejunum and then declining in the ileum and colon. This non-uniform distribution of CYP3A causes regional variability in the absorption of drugs that are substrates to these enzymes (Chawla et al., 2003).

2.11.4 Factors affecting performance of gastroretentive system

Various attempts have been made to increase the retention time of the dosage forms in the stomach. These attempts include floating dosage forms (gas-generating systems and swelling or expanding systems), mucoadhesive systems, high-density systems, modified shape systems, gastric-emptying delaying devices and co-administration of gastric-emptying delaying drugs (Garg and Sharma, 2003). However,
most of these approaches are influenced by a number of factors that affect their efficacy as a GR system (Sampat et al., 2009).

- Density: Gastric retention time (GRT) is a function of dosage form buoyancy that is dependent on the density.
- Size: dosage form units with a diameter of more than 13 mm are reported to have an increased GRT (Streubel et al., 2006).
- Shape of dosage form: tetrahedron and ring shaped devices with a flexural modulus of 48 and 22.5 kilo pounds per square inch (KSI) are reported to have better GRT ≈90% to 100% retention at 24 h compared with other shapes.
- Single or multiple unit formulation: multiple unit formulations show a more predictable release profile, allow co-administration of units with different release profiles or containing incompatible substances and permit a larger margin of safety against dosage form failure compared with single unit dosage forms.
- Fed or fasted state: under fasting conditions, the GI motility is characterized by periods of strong motor activity or the migrating myoelectric complex (MMC) that occurs every 1.5 to 2 h. The MMC sweeps undigested material from the stomach and, if the timing of administration of the formulation coincides with that of the MMC, the GRT of the unit can be expected to be very short. However, in the fed state, MMC is delayed and GRT is considerably longer.
- Nature of meal: feeding of indigestible polymers or fatty acid salts can change the motility pattern of the stomach to a fed state, thus decreasing the gastric emptying rate and prolonging drug release.
- Caloric content: GRT can be increased by 4 to 10 h with a meal that is high in proteins and fats.
- Frequency of feed: the GRT can increase by over 400 min when successive meals are given compared with a single meal due to the low frequency of MMC.
• Gender: mean ambulatory GRT in males (3.4±0.6 h) is less compared with their age and race matched female counterparts (4.6±1.2 h), regardless of the weight, height and body surface.
• Age: elderly people, especially those over 70, have a significantly longer GRT.
• Posture: GRT can vary between supine and upright ambulatory states of the patient.
• Concomitant drug administration: anticholinergics like propantheline and atropine, opiates like codeine and prokinetic agents like metoclopramide and cisapride.

2.11.5 Pharmacokinetic and pharmacodynamic advantages of GRDDS

Incorporation of the drug in a GRDDS can yield significant therapeutic advantages due to a variety of pharmacokinetic (PK) and pharmacodynamic (PD) factors (Jain et al., 2005; Hoffman et al., 2004).

2.11.5.1 Pharmacokinetic aspects

Absorption window: It implies validation that the drug is within the category of narrow absorption window agents. Currently, various techniques are available that permit us to verify the absorption properties of the tested molecule, to determine the mechanism of intestinal absorption, and to elucidate the permeability at different regions of the GI tract. In general, appropriate candidates for GRDDS are molecules that have poor colonic absorption but are better absorbed at the upper parts of the GI tract like stomach, duodenum or jejunum. In case of absorption by active transporters that are capacity limited, the efficacy of transport may increase following sustained presentation of the drug to the transporting enzymes in comparison to non-GR mode of administration.

Enhanced bioavailability: The bioavailability of riboflavin and levodopa GRDDS is significantly enhanced in comparison to administration of non-GRDDS formulations. It may be concluded that several different processes, related to absorption and transit of the drug in the GIT, act concomitantly and influence the magnitude of drug absorption. Therefore, in-vivo studies are
necessary to determine the release profile of the drug from the dosage form that will provide enhanced BA.

*Enhanced first-pass biotransformation:* In a similar fashion to increased efficacy of active transporters exhibiting capacity-limited activity, the presystemic metabolism of the tested compound may be considerably increased when the drug is presented to the metabolic enzymes (cytochrome P450, in particular CYP3A4) in a sustained manner, rather than by a bolus input.

*Improved bioavailability due to reduced P-glycoprotein (P-gp) activity in the duodenum:* In apparent contrast to the higher density of CYP3A4 at the upper part of the intestine, P-gp mRNA levels increase longitudinally along the intestine such that the highest levels are located in the colon. Therefore, for drugs that are P-gp substrate and do not undergo oxidative metabolism, such as digoxin, GRDDS may elevate absorption compared to the immediate and CR dosage forms.

*Reduced frequency of dosing:* For drugs with a relatively short $t_{1/2}$, sustained and slow input from GRDDS may result in a flip-flop pharmacokinetics and enable reduced dosing frequency. This feature is associated with improved patient compliance, and thereby improves therapy.

*Targeted therapy for local ailments in the upper GIT:* The prolonged and sustained administration of the drug from the GRDDS to the stomach may be advantageous for local therapy in the stomach and the small intestine. By this mode of administration, therapeutic drug concentrations may be attained locally, while the systemic concentrations, following drug absorption and distribution, are minimal.

### 2.11.5.2 Pharmacodynamic aspects

*Reduced fluctuations of drug concentration:* Continuous input of the drug following CR-GRDF administration produces blood drug concentrations within a narrower range compared to the IR dosage forms. Thus, fluctuations in drug effects are minimized, and concentration-dependent adverse effects that are associated with peak concentrations can be prevented. This feature is of special importance for drugs with a narrow therapeutic index.
**Improved selectivity in receptor activation:** Minimization of fluctuations in drug concentration also makes it possible to obtain certain selectivity in the elicited pharmacological effect of drugs that activate different types of receptors at different concentrations.

**Reduced counter-activity of the body:** In many cases, the pharmacological response, which intervenes with the natural physiologic processes, provokes a rebound activity of the body that minimizes drug activity. Slow input of the drug into the body was shown to minimize the counter-activity leading to higher drug efficiency.

**Extended time over critical (effective) concentration:** For certain drugs that have non-concentration-dependent pharmacodynamics, such as beta-lactam antibiotics, the clinical response is not associated with peak concentration, but rather, with the duration of time over a critical therapeutic concentration. The sustained mode of administration enables extension of the time over a critical concentration and thus enhances the pharmacological effects and improves the clinical outcomes.

**Minimized adverse activity at the colon:** Retention of the drug in the GRDF at the stomach minimizes the amount of drug that reaches the colon. Thus, undesirable activities of the drug in colon may be prevented. This PD aspect provides the rationale for GRDF formulation for beta-lactam antibiotics that are absorbed only from the small intestine, and whose presence in the colon leads to the development of microorganism’s resistance.

In most cases, due to complexity of PK and PD parameters, the *in-vivo* studies are required to establish the optimal dosage form for a specific drug. For a certain drug, interplay of its PK and PD parameters will determine the effectiveness and benefits of the CR-GRDF compared to the other dosage forms.

### 2.12 Gastroretentive Strategies

There are numerous methods which are reported in the literature through which gastroretention can be achieved. The main strategies are listed below:

1. High density systems or sinking systems
2. Magnetic systems
3. Superporous hydrogel systems
4. Swellable/expandable drug delivery systems
5. Mucoadhesive drug delivery systems
6. Floating drug delivery systems or low density systems

2.12.1 High density systems

The high density systems which are meant for gastroretention relies on density of contents of stomach which is normally close to the density of water (1.004 g/cm$^3$). These systems exhibit gastroretention because of the high density due to which they sink to the bottom of the stomach as depicted in Figure 2.7. The threshold density is approximately 2.4-2.8 g/cm$^3$ for retaining systems in the lower part of stomach (Rouge et al., 1998). These systems are usually prepared by coating drug on heavy core or mixed with high density inert materials like iron powder, barium sulphate, zinc oxide and titanium oxide etc. (Vyas and Khar, 2006).

![Figure 2.7: Functioning of high density systems (Bardonnet et al., 2006)](image)

2.12.2 Magnetic systems

In this type of system, small internal magnet is incorporated in the delivery system. After administration of this delivery system, a magnet is placed over the abdomen which helps in guiding and retaining the delivery system in the stomach only. However this approach is less applied or tried due to possible reason of patient compliance in terms of placing the external magnet over the abdomen that too at exact position (Hwang et al., 1998).
2.12.3 Superporous hydrogel systems

These hydrogels systems appear to be similar or one of the types of swellable or expandable systems but they differ from conventional hydrogels because conventional hydrogel takes up water rather slowly than superporous hydrogels (Pawar et al., 2011). The main reason for this is the difference in the pore size, conventional hydrogels have pore size between 10 nm to 10 µm and several hours may be needed to reach an equilibrium state during which premature evacuation of the dosage form may occur while the average pore size for superporous hydrogels is greater than 100 µm due to which they uptake water by capillary wetting through numerous interconnected open pores resulting in the large size still having sufficient mechanical strength to withstand pressure generated by gastric contractions (Park et al., 2005).

2.12.4 Swellable or expandable systems

These are small in size which is a pre-requisite for convenient oral intake. But as soon as they come in contact with aqueous gastric fluid, they swell or expand many folds, a property imparted by special swellable materials or the polymers included in these types of systems which will hinder their evacuation from stomach through pyloric sphincter (Figure 2.8). So they remain in the stomach for a prolonged period of time, release the drug and get slowly eroded overtime.

Figure 2.8: Swellable gastroretentive systems (Gutierrez-Rocca et al., 2003)

2.12.5 Mucoadhesive Drug Delivery Systems

Bioadhesion may be defined as the state in which two materials, at least one of which is of biological nature, are held together for extended periods of time by
interfacial forces (Good, 1983). If biological membrane is mucus membrane, then the process of adhesion is called mucoadhesion. Mucoadhesion is widely reported phenomenon for achieving site-specific drug delivery through the incorporation of mucoadhesive polymers within formulation along with the active drug. The formulation will adhere to the mucosal surface for extended period of time for localized drug delivery and facilitate an intimate contact of the dosage form with the underlining absorption surface and thus contribute to improved and better therapeutic performance of the drug (Asane et al., 2007).

2.12.5.1 Mucoadhesion theories

There are six general theories of adhesion, which have been adapted for the investigation of mucoadhesion (Smart, 2005a; Salamat-Miller et al., 2005; Sudhakar et al., 2006; Andrews et al., 2009).

1. Electronic Theory: According to the electronic theory, electron transfer occurs upon contact of an adhesive polymer with a mucus glycoprotein network because of differences in their electronic structures. This results in the formation of an electrical double layer at the interface. Adhesion occurs due to attractive forces across the double layer.

2. Wetting Theory: This theory is predominantly applicable to liquid bioadhesive systems and considers surface and interfacial energies. It describes the affinity of a bioadhesive polymer to spread on biological surfaces and the affinity of a liquid for a surface can be found using techniques such as contact angle goniometry to measure the contact angle of the liquid surface, with the general rule being that the lower the contact angle, the greater the affinity of the liquid to the solid. The spreading coefficient ($S_{AB}$) can be calculated from the surface energies of the solid and liquids using the equation:

$$S_{AB} = \gamma_B - \gamma_A - \gamma_{AB}$$

Where $\gamma_A$ is the surface tension (energy) of the liquid A, $\gamma_A$ is the surface energy of the solid B and $\gamma_{AB}$ is the interfacial energy between the solid and liquid. $S_{AB}$ should be positive for the liquid to spread spontaneously over the solid.
Chapter 2—Review of Literature

The work of adhesion \( (w_A) \) represents the energy required to separate the two phases, and is given by:

\[
w_A = \gamma_A + \gamma_B - \gamma_{AB}
\]

The greater the individual surface energies of the solid and liquid relative to the interfacial energy, the greater the work of adhesion.

3. Adsorption Theory: According to the adsorption theory, after an initial contact between two surfaces, the material adheres because of surface forces acting between the atoms in the two surfaces. Two types of chemical bonds resulting from these forces can be distinguished:

- Primary chemical bonds of covalent nature, which are undesirable in bioadhesion because their high strength may result in permanent bonds.
- Secondary chemical bonds having many different forces of attraction, including electrostatic forces, vander Waals forces, hydrogen and hydrophobic bonds.

4. Diffusion Theory: The basis of the diffusion theory is chain entanglement between glycoproteins of the mucus and the mucoadhesive polymer (Figure 2.9). Upon initial contact between these two polymers, diffusion of the bioadhesive polymer chain into the mucus network creates an entangled network between the two polymers. Sufficient polymer chain flexibility, adequate exposure for the surface contact of both polymers, similar chemical structures, and the diffusion coefficient of the bioadhesive polymer are among the factors which influence the inter-diffusion of the macromolecule network.

![Figure 2.9: Diffusion through interpenetration of bioadhesive and mucus polymer chains (Carvalho et al., 2010).](image-url)
5. Mechanical Theory: The mechanical theory assumes that adhesion arises from an interlocking of a liquid adhesive (on setting) into irregularities on a rough surface. However, rough surfaces also provide an increased surface area available for interaction along with an enhanced viscoelastic and plastic dissipation of energy during joint failure, which are thought to be more important in the adhesion process than a mechanical effect (Peppas and Sahlin, 1996).

6. Fracture Theory: According to this theory, the adhesive bond between systems is related to the force required to separate both surfaces from one another. This “fracture theory” relates the force for polymer detachment from the mucus to the strength of their adhesive bond. The work of fracture has been found to be greater when the polymer network strands are longer or if the degree of cross-linking within such system is reduced (Ahagon and Gent, 1975). This theory allows the determination of fracture strength (σ) following the separation of two surfaces via its relationship to Young’s modulus of elasticity (E), the fracture energy (e) and the critical crack length (L) through the following equation (Gu et al., 1988):

\[ \sigma = \left( \frac{Ee}{L} \right)^{1/2} \]

2.12.5.2 Mechanism of mucoadhesion

The mechanism of adhesion of certain macromolecules to the surface of a mucous tissue is not well understood yet. The mucoadhesive must spread over the substrate to initiate close contact and increase surface contact, promoting the diffusion of its chains within the mucus. Attraction and repulsion forces arise and, for a mucoadhesive to be successful, the attraction forces must dominate. The mechanism of mucoadhesion is generally divided into two stages, the contact stage and the consolidation stage (Figure 2.10). The first stage is characterized by the contact between the mucoadhesive and the mucous membrane, with spreading and swelling of the formulation, initiating its deep contact with the mucus layer (Hagerstrom et al., 2003).
In the consolidation step, the mucoadhesive materials are activated by the presence of moisture. Moisture plasticizes the system, allowing the mucoadhesive molecules to break free and to link up by weak Vander Waals forces and hydrogen bonds. Essentially, there are two theories explaining the consolidation step: the diffusion theory and the dehydration theory. According to diffusion theory, the mucoadhesive molecules and the glycoproteins of the mucus mutually interact by means of interpenetration of their chains (Figure 2.9) and the building of secondary bonds (Smart, 2005b). For this to take place the mucoadhesive device must have features favoring both chemical and mechanical interactions. Therefore, molecules with hydrogen bonds building groups (–OH, –COOH), with an anionic surface charge, high molecular weight, flexible chains and surface-active properties, which induct its spread throughout the mucus layer, can present mucoadhesive properties (Mathiowitz and Chickering, 1999).

According to dehydration theory, materials that are able to readily form gel in an aqueous environment, when placed in contact with the mucus can cause its dehydration due to the difference of osmotic pressure. The difference in concentration gradient draws the water into the formulation until the osmotic balance is reached (Figure 2.11). This process leads to the mixture of formulation and mucus and can thus increase contact time with the mucous membrane. Therefore, it is the water motion that leads to the consolidation of the adhesive bond, and not the interpenetration of macromolecular chains. However, the dehydration theory is not applicable for solid formulations or highly hydrated forms (Smart, 2005b; Carvalho et al., 2010).
2.12.5.3 Factors affecting mucoadhesion

Mucoadhesive characteristics are a factor of both the bioadhesive polymer and the medium in which the polymer will reside. A variety of factors that affect the mucoadhesive properties of polymer are listed in Table 2.4 (Vasir et al., 2003; Smart, 2005b; Salamat-Miller et al., 2005; Andrews et al., 2009):

Table 2.4: Factors affecting mucoadhesion.

<table>
<thead>
<tr>
<th>Factor</th>
<th>Characteristics</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Polymer related factors</strong></td>
<td></td>
</tr>
<tr>
<td>Molecular weight</td>
<td>Properties of the Mucoadhesive polymer</td>
</tr>
<tr>
<td></td>
<td>Low molecular weight: favours the interpenetration of polymer molecules</td>
</tr>
<tr>
<td></td>
<td>High molecular weight: favours physical entanglement</td>
</tr>
<tr>
<td></td>
<td>Optimum molecular weight: at least 100,000 (threshold)</td>
</tr>
<tr>
<td>Polymer chain flexibility</td>
<td>Required for interpenetration and entanglement</td>
</tr>
<tr>
<td>Hydrogen bonding capacity</td>
<td>Presence of functional groups those are able to form hydrogen bonds (COOH, OH, etc.).</td>
</tr>
<tr>
<td>Cross linking density</td>
<td>With increasing density of cross-linking, diffusion of water into the polymer network occurs at a lower rate which, in turn, causes an insufficient swelling of the polymer and a decreased rate of interpenetration between polymer and mucin.</td>
</tr>
<tr>
<td>Concentration</td>
<td>Affects the availability for penetration of long polymer chains into the mucus layer; important mainly for liquid and viscous DDS.</td>
</tr>
<tr>
<td>Charge</td>
<td>Peppas and Buri have demonstrated that strong anionic charge on the polymer is one of the required characteristics for mucoadhesion. Some generalizations about the charge have been made where anionic polymers undergo &gt; degree of adhesion than cationic polymers and cationic polymers &gt; neutral polymers.</td>
</tr>
<tr>
<td>Degree of hydration (swelling)</td>
<td>Hydration is essential for the relaxation and interpenetration of polymer chains, Excess hydration could lead to decreased mucoadhesion and/or retention due to the formation of slippery mucilage.</td>
</tr>
</tbody>
</table>

Contd...
Table 2.4 Contd…: Factors affecting mucoadhesion.

<table>
<thead>
<tr>
<th>Factor</th>
<th>Characteristics</th>
</tr>
</thead>
<tbody>
<tr>
<td>Spatial conformation</td>
<td>Besides molecular weight or chain length, spatial conformation of a molecule is also important. Despite a high molecular weight of 19,500,000 for dextrans, they have adhesive strength similar to that of PEG, with a molecular weight of 200,000. The helical conformation of dextran may shield many adhesively active groups, primarily responsible for adhesion, unlike PEG polymers, which have a linear conformation.</td>
</tr>
</tbody>
</table>

**Environmental factors**

<table>
<thead>
<tr>
<th>Factor</th>
<th>Characteristics</th>
</tr>
</thead>
<tbody>
<tr>
<td>pH</td>
<td>Changes in pH lead to differences in the extent of dissociation of functional groups in carbohydrate sequences or polypeptide amino acid sequences, as well as in the polymer.</td>
</tr>
<tr>
<td>Pressure applied to the system for attachment</td>
<td>Affects the depth of diffusion of chains.</td>
</tr>
<tr>
<td>Duration of initial contact</td>
<td>Determines the extent of swelling and diffusion of polymer chains.</td>
</tr>
<tr>
<td>Moistening</td>
<td>Moistening is required to allow the mucoadhesive polymer to spread over the surface and create a “macromolecular network” of sufficient size for the interpenetration of polymer and mucin molecules and to increase the mobility of polymer chains. However, there is a critical level of hydration for mucoadhesive polymers characterized by optimum swelling and bioadhesion.</td>
</tr>
<tr>
<td>Presence of metal ions</td>
<td>Interaction with charged groups of polymers and/or mucus can decrease the number of interaction sites and the tightness of mucoadhesive bonding.</td>
</tr>
</tbody>
</table>

**Physiological factors**

<table>
<thead>
<tr>
<th>Factor</th>
<th>Characteristics</th>
</tr>
</thead>
<tbody>
<tr>
<td>Rate of renewal of mucosal cells</td>
<td>Varies extensively for different types of mucosa. Limits the persistence of bioadhesive systems on mucosal surfaces.</td>
</tr>
<tr>
<td>Concomitant diseases</td>
<td>Can alter the physicochemical properties of mucus or its quantity (for example, hypo and hypersecretion of gastric juice). Increases in body temperature, ulcer disease, colitis, tissue fibrosis, allergic rhinitis, bacterial or fungal infection, and inflammation.</td>
</tr>
<tr>
<td>Tissue movement</td>
<td>On consumption of liquid and food, speaking, peristalsis in the GIT.</td>
</tr>
</tbody>
</table>

**2.12.5.4 Classification of mucoadhesive polymers**

Polymers are very long molecules consisting of structural units and repeating units connected by covalent chemical bonds. The term is derived from the Greek words: *polys* meaning many, and *meros* meaning parts. The key feature that
distinguishes polymers from other molecules is the repetition of many identical, similar, or complementary molecular subunits in these chains. These subunits, the monomers, are small molecules of low to moderate molecular weight, and are linked to each other during a chemical reaction called polymerization. Instead of being identical, similar monomers can have varying chemical substituents. The differences between monomers can affect properties such as solubility, flexibility and strength.

Mucoadhesive formulations use polymers as the adhesive component. These formulations are often water soluble and when in a dry form attract water from the biological surface and this water transfer leads to a strong interaction. These polymers also form viscous liquids when hydrated with water that increases their retention time over mucosal surfaces and may lead to adhesive interactions.

Mucoadhesive polymers are water-soluble or water-insoluble polymers, which are swellable networks, joined by cross-linking agents. These polymers possess optimal polarity to make sure that they permit sufficient wetting by the mucus and optimal fluidity that permits the mutual adsorption and interpenetration of polymer and mucus to take place. Mucoadhesive polymers that adhere to the mucin-epithelial surface can be conveniently divided into three broad classes (Park and Robinson, 1984):

1. Polymers that become sticky when placed in water and owe their mucoadhesion to stickiness.
2. Polymers that adhere through nonspecific, non-covalent interactions those are primarily electrostatic in nature (although hydrogen and hydrophobic bonding may be significant).
3. Polymers that bind to specific receptor sites on the cell surface.

All three polymer types can be used for drug delivery.

In general, adhesive polymers can be classified as synthetic vs. natural, water-soluble vs. water insoluble, and charged vs. uncharged polymers (Salamat-Miller et al., 2005; Muthukumaran et al., 2011; Roge et al., 2011). Classification of the mucoadhesive polymers is listed in Table 2.5.
Table 2.5: Classification of mucoadhesive polymers.

<table>
<thead>
<tr>
<th>Criteria</th>
<th>Categories</th>
<th>Examples</th>
</tr>
</thead>
<tbody>
<tr>
<td>Source</td>
<td>Semi-natural/natural</td>
<td>Agarose, chitosan, gelatin, Hyaluronic acid, Various gums (guar, hakea, xanthan, gellan, tragacanth, karaya, carragenan, pectin, and sodium alginate)</td>
</tr>
<tr>
<td></td>
<td>Synthetic</td>
<td>Cellulose derivatives: CMC, thiolated CMC, sodium CMC, HEC, HPC, HPMC, MC, methylhydroxyethylcellulose</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Poly(acrylic acid)-based polymers: CP, PC, PAA, polyacrylates, poly(methylvinylether-co-methacrylic acid), poly(2-hydroxyethyl methacrylate), poly(acrylic acid-co-ethylhexylacrylate), poly(methacrylate), poly(alkylcyanoacrylate), poly(isohexylcyanoacrylate), poly(isobutylcyanoacrylate), copolymer of acrylic acid and PEG</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Others: Polyethylene oxide, PVA, PVP, thiolated polymers</td>
</tr>
<tr>
<td>Aqueous solubility</td>
<td>Water-soluble</td>
<td>HEC, HPC, HPMC, PAA, sodium CMC, sodium alginate</td>
</tr>
<tr>
<td></td>
<td>Water-insoluble</td>
<td>Chitosan (soluble in dilute aqueous acids), EC, PC, CP</td>
</tr>
<tr>
<td>Charge</td>
<td>Cationic</td>
<td>Aminodextran, chitosan, dimethylaminoethyl (DEAE)-dextran, trimethylated chitosan</td>
</tr>
<tr>
<td></td>
<td>Anionic</td>
<td>Chitosan-EDTA, CP, CMC, pectin, PAA, PC, sodium alginate, sodium CMC, xanthan gum</td>
</tr>
<tr>
<td></td>
<td>Neutral</td>
<td>Hydroxypropyl cellulose, eudragit analogues</td>
</tr>
<tr>
<td>Potential bioadhesive forces</td>
<td>Covalent</td>
<td>Cyanoacrylate</td>
</tr>
<tr>
<td></td>
<td>Hydrogen bond</td>
<td>Acrylates [hydroxylated methacrylate, poly(methacrylic acid)], CP, PC, PVA</td>
</tr>
<tr>
<td></td>
<td>Electrostatic interaction</td>
<td>Chitosan</td>
</tr>
</tbody>
</table>

CMC-Carboxymethyl cellulose; HEC-Hydroxyethyl cellulose; HPC-Hydroxypropyl cellulose; HPMC-Hydroxypropyl methylcellulose; MC-Methylcellulose; PVA-Polyvinyl alcohol; PVP-Polyvinylpyrrolidone; CP-Carbopol; PC-Polycarbophil; PAA-Polyacrylic acid; EC-Ethylcellulose.
2.12.5.5 Characteristics of an ideal mucoadhesive polymer

- Cationic and anionic polymers bind more effectively than neutral polymers.
- Anionic polymers with sulfate groups bind more effectively than those with carboxylic groups.
- Polyanions are better than polycations in terms of binding potential and toxicity.
- Should adhere to mucosa and should possess sufficient mechanical strength.
- Water-insoluble polymers give greater flexibility in dosage form design compared to rapidly or slowly dissolving water-soluble polymers.
- It should preferably form a strong non-covalent bond with the mucin-epithelial cell surfaces.
- Should possess some site-specificity.
- pH should be biocompatible and should possess good viscoelastic properties.
- It should allow incorporation to the drug and offer no hindrance to tailor the release of the drug.
- Polymer and its degradation products should be non-toxic, non-irritant and free from leachable impurities.
- Should have good wetting, swelling, solubility and biodegradability properties.
- Should show bioadhesive properties in both dry and liquid state.
- Should demonstrate acceptable shelf life.

Ideal molecular characteristics

Characteristics of representative mucoadhesive polymers are provided in Table 2.6. Investigations into polymers with various molecular characteristics conducted by many authors (Park and Robinson, 1984; Smart et al., 1984) have led to a number of conclusions regarding the molecular characteristics required for mucoadhesion. The properties exhibited by a good mucoadhesive polymer may be summarized as follows (Peppas and Buri, 1985):
• Strong hydrogen bonding groups (-OH, -COOH).

• Strong anionic charges.

• Sufficient flexibility to penetrate the mucus network or tissue crevices.

• Surface tension characteristics suitable for wetting mucus/mucosal tissue surface.

• High molecular weight.

• Although an anionic nature is preferable for a good mucoadhesive, a range of nonionic molecules (e.g., cellulose derivatives) and some cationic (e.g., Chitosan) can be successfully used.
### Table 2.6: Properties and characteristics of some representative mucoadhesive polymers (Sudhakar et al., 2006)

<table>
<thead>
<tr>
<th>Bioadhesive</th>
<th>Properties</th>
<th>Characteristics</th>
</tr>
</thead>
<tbody>
<tr>
<td>Carbopol/carbomer (carboxy polymethylene)</td>
<td>Pharmaceutical grades: 934 P, 940 P, 971 P and 974 P. Mw 1×10^6–4×10^6 Viscosity 29,400–39,400 cps at 25°C with 0.5% neutralized aqueous solution. Density 5 g/cm^3 in bulk, 1.4 g/cm^3 tapped. pH 2.5–3.0 Soluble in water, alcohol, glycerin.</td>
<td>Excellent thickening, emulsifying, suspending, gelling agent. They swell in water. Up to 1000 times their original volume to form a gel when exposed to a pH of 4.0 to 6.0. Common component in bioadhesive dosage forms. Gel loses viscosity on exposure to sunlight. Unaffected by temperature variations, hydrolysis, oxidation and resistant to bacterial growth.</td>
</tr>
<tr>
<td>Hydroxypropyl methylcellulose (Hypromellose, HPMC)</td>
<td>Methocel E5, E15, E50, E4M, F50, F4M, K100, K4M, K15M, K100M. Mw 8.6×10^4 Viscosity E5–15 cps, E4M–400 cps and K4M–4000 cps (2% aqueous solution.) Soluble in water</td>
<td>Suspending, viscosity-increasing and film forming agent. Tablet binder and adhesive ointment ingredient. E grades are generally suitable as film formers. While the K grades are used as thickeners. Solutions are stable at pH 3.0 to 11.0</td>
</tr>
<tr>
<td>Polycarbophil (polyacrylic acid crosslinked with divinyl glycol)</td>
<td>Mw 2.2×10^5 Viscosity 2000–22,500 cps (1% aq. soln.) Insoluble in water, but swell to varying degrees in common organic solvents, strong mineral acids and bases</td>
<td>Swellable depending on pH and ionic strength. Swelling increases as pH increases. Entangle the polymer with mucus on the surface of the tissue Hydrogen bonding between the nonionized carboxylic acid and mucin.</td>
</tr>
</tbody>
</table>

Contd...
Table 2.6 Contd…: Properties and characteristics of some representative mucoadhesive polymers (Sudhakar et al., 2006)

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<th>Biodhesive</th>
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| Polycarbophil (polyacrylic acid crosslinked with divinyl glycol) | Mw $2.2 \times 10^5$  
Viscosity 2000–22,500 cps (1% aq. soln.)  
Insoluble in water, but swell to varying degrees in common organic solvents, strong mineral acids and bases | Swellable depending on pH and ionic strength.  
Swelling increases as pH increases.  
Entangle the polymer with mucus on the surface of the tissue  
Hydrogen bonding between the nonionized carboxylic acid and mucin. |
| Hydroxypropyl cellulose (HPC) (non-ionic polymer) | Grades: Klucel EF, LF, JF, GF, MF and HF  
Mw $6 \times 10^4$–$1 \times 10^6$  
Viscosity 4–6500 cps with 2.0% aq. soln.  
pH 5.0–8.0  
Soluble in water below 38 °C and Insoluble in hot water. | Solutions of HPC are susceptible to shear, heat, bacterial, enzymatic and bacterial degradation.  
Inert, no skin irritation or sensitization.  
Compatible with most water-soluble gums and resins.  
Not metabolized in the body.  
Granulating and film coating agent for tablet.  
Thickening agent, Stabilizer, suspending agent in oral and topical solution or suspension. |
| Sodium Alginate (anionic polymer) | Viscosity 20–400 Cps (1% aqueous solution.)  
Soluble in Water, forming a viscous, colloidal solution. | Stabilizer in emulsion, suspending agent, tablet disintegrant, tablet binder.  
Excellent gel formation properties.  
Biocompatible.  
Lacks yield value.  
Compatible with most water-soluble thickeners and resins. |
Table 2.6 Contd…: Properties and characteristics of some representative mucoadhesive polymers (Sudhakar et al., 2006)

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<th>Bioadhesive</th>
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<tr>
<td>Sodium carboxymethyl cellulose (SCMC)</td>
<td>Grades H, M, and L Mw $9 \times 10^4$–$7 \times 10^5$ Viscosity 1200 cps with 1.0% solution Density 0.75 g/cm$^3$ in bulk pH 6.5–8.5</td>
<td>Emulsifying, gelling, binding agent. Stable on storage. Incompatible with strongly acidic solutions. CMC solutions offer good tolerance of water-miscible solvents, good viscosity stability over the pH 4 to pH 10 range, and compatibility with most water soluble nonionic gums. All solutions show a reversible decrease in viscosity at elevated temperatures.</td>
</tr>
<tr>
<td>Guar gum (Galactomannan polysaccharide)</td>
<td>Mw approx. 220,000 Viscosity 2000–22500 Cps (1% aqueous solution). Forms viscous colloidal solution when hydrated in cold water. The optimum rate of hydration is between pH 7.5 and 9.0.</td>
<td>Stable in solution over a pH range of 1.0–10.5. Prolonged heating degrades viscosity. Incompatible with acetone, tannins, strong acids, and the alkalis. Used as thickener for lotions and creams, as tablet binder, and as emulsion stabilizer.</td>
</tr>
<tr>
<td>Xanthan gum (Anionic Polymer)</td>
<td>It is soluble in hot or cold water and gives visually hazy, neutral pH solutions. Viscosity 1500 to 2500 cps (1% aqueous solution). Solutions possess excellent yield value.</td>
<td>Xanthan gum is more tolerant of electrolytes, acids and bases than most other organic gums. It can, nevertheless, be gelled or precipitated with certain polyvalent metal cations under specific circumstances. It is more compatible with most nonionic and anionic gums.</td>
</tr>
</tbody>
</table>
Table 2.6 Contd…: Properties and characteristics of some representative mucoadhesive polymers (Sudhakar et al., 2006)

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<td>Chitosan (cationic polymer)</td>
<td>Soluble in dilute acids to produce a linear polyelectrolyte with a high positive charge density and forms salts with inorganic and organic acids such as glutamic acid, hydrochloric acid, lactic acid, and acetic acid.</td>
<td>Mucoadhesive agent due to either secondary chemical bonds such as hydrogen bonds or ionic interactions between the positively charged amino groups of chitosan and the negatively charged sialic acid residues of mucus glycoproteins or mucins. Possesses cell-binding activity due to polymer’s cationic polyelectrolyte structure and to the negative charge of the cell surface. Biocompatible and biodegradable. Excellent gel forming and film forming ability. Widely used in controlled delivery systems such as gels, membranes, microspheres. It enhances the transport of polar drugs across epithelial surfaces.</td>
</tr>
<tr>
<td>Thiolated polymers</td>
<td>Derived from hydrophilic polymers such as polyacrylates, chitosan or deacetylated gellan gum. Mucoadhesive ability at physiological pH values.</td>
<td>Capable of forming disulfide bonds with cysteine-rich subdomains of mucus glycoproteins covering mucosal membranes. Strongest mucoadhesive properties of all so far tested polymeric excipients. Improved tensile strength, high cohesive properties, rapid swelling, and water uptake behavior.</td>
</tr>
</tbody>
</table>
2.12.6 Floating drug delivery systems (FDDS)

The concept of floating drug delivery systems (FDDS) for gastroretention is very simple in which the underlying principle is to make the density of delivery system less than that of the gastric fluids due to which it can float on the surface of gastric fluids. Numerous techniques have been employed to develop an ideal floating delivery system (Kotreka and Adeyeye, 2011). The various buoyant preparations include hollow microspheres (microballoons), granules, powders, capsules and tablets. Single-unit systems are most commonly reported floating systems in literature, such as the hydrodynamically balanced systems (HBS) (Dorozynski et al., 2004) and floating tablets. While the system is floating on the gastric contents present in the stomach, the drug is released slowly at the predetermined rate from the formulation (Sampat et al., 2009). After release of drug, the residual system is emptied from the stomach to the next part of GIT. This results in an increased GRT, which could improve BA, reduce drug wastage and result in a better control of fluctuations in the plasma drug concentrations (El-Gamal et al., 2011). The presence or absence of food also influences the gastric emptying time. Gastric emptying is much more rapid in the fasting state and floating systems rely heavily on the presence of food to retard emptying (Mazer et al., 1988) and provide sufficient liquid for effective buoyancy (Singh and Kim, 2000).

An FDDS either floats over gastric fluids due to its lower density than the stomach contents or due to its inherently lower density or the gaseous phase formed inside the system after it comes in contact with the gastric environment. Non-effervescent and effervescent systems are the two different technologies which have been utilized in the development of FDDS and are based on the mechanism of buoyancy.

2.13.6.1 Non-effervescent systems

Non-effervescent floating properties of DDS can be based on several principles, including low density due to swelling and inherent low density:

Low density due to swelling

By imbibing the fluid present in the stomach, this type of systems swells abundantly to cease its exit from the stomach. The appropriate amount of drug mixed with the gel which when comes in contact with gastric fluid after administration
maintains a bulk density of <1 g cm\(^{-3}\) and also maintains the physical integrity. These systems also have a tendency to remain lodged near the pyloric system also known as the ‘plug- type system’. The air entrapped by the swollen polymer confers buoyancy to these dosage forms.

*Hydrodynamically balanced system (HBS)*

This sustained release, floating single unit dosage form consists of a capsule, which contains a mixture of drug and hydrocolloids (Ali *et al.*, 2007). Hydrodynamically balanced systems (HBS) are suitable for drugs having a better solubility in an acidic environment and also for the drugs having a specific site of absorption in the upper part of the small intestine (Rocca *et al.*, 2003). Matrix tablets based on HPMC K4M have also been developed. Following contact with gastric fluid, the systems take up water and swell. As the increase in volume is more important than the increase in mass during swelling, the densities of these devices decreases, acquiring a value of < 1. Thus, after a certain lag time the systems start to float. The influence of several processing and formulation parameters on the floating properties of this type of matrix tablet has been studied by different research groups (Park *et al.*, 2011). Recently a glyceryl mono oleate (GMO) matrix was proposed as a GR carrier system (Kumar *et al.*, 2004). The devices were prepared by melting GMO at 55°C in a water bath, adding the drug under stirring and pouring the molten mass into cylindrical moulds with an inner diameter of 8.5 mm. The GMO matrices significantly swelled in water and the swollen masses floated at the surface after a certain lag time. Drug release is controlled by the formation of a hydrated boundary at the surface. Continuous erosion of the surface allows water penetration to the inner layers, maintaining surface hydration and buoyancy. These systems incorporate a high level (20-75% w/w) of one or more gel-forming, highly swellable, cellulose-type hydrocolloids e.g., hydroxypropyl methylcellulose (HPMC), hydroxyethyl cellulose (HEC), sodium carboxymethyl cellulose (NaCMC), polysaccharides and matrix forming polymers such as polycarbophil, polyacrylates and polystyrene.

On coming in contact with gastric fluid, the hydrocolloid in the system hydrates and forms a colloidal gel barrier around its surface. This gel barrier controls the rate of fluid penetration into the device and the consequent release of the drug by diffusion and erosion of the gel barrier as depicted in Figure 2.12. The main drawback
is that the operation is dependent on the air sealed in the central dry mass within the hydrated gelatinous surface layer and hence on the characteristics and amount of polymer. As the exterior surface of the dosage form goes into the solution, the gel layer is maintained by the adjacent hydrocolloid layer becoming hydrated. The air entrapped in the swollen polymer maintains a density less than unity and confers buoyancy to these dosage forms.

Figure 2.12: The gelatinous polymer barrier formation as a result from hydrophilic polymer swelling in HBS

The HBS must comply with three major criteria (Ali et al., 2007):

- It must maintain an overall specific gravity lower than that of gastric contents.
- It must have sufficient structure to form a cohesive gel barrier.
- It should dissolve slowly enough to serve as a “reservoir” for the delivery system.

A bilayer tablet can also be prepared to contain one IR and other SR layer. IR layer delivers the initial dose, whereas SR layer absorbs gastric fluid and forms a colloidal gel barrier on its surface. A bilayer formulation of misoprostol against gastric ulcers was prepared by Oth et al. (1992).

*Intragastric floating gastrointestinal drug delivery devices*

This technology is based on the encapsulation of a drug reservoir inside a micro porous compartment with apertures along its top and bottom walls, as shown in Figure 2.13. Any direct contact of the gastric mucosal surface with the undissolved drug is prevented by sealing of peripheral walls of the drug reservoir compartment. In
stomach, the floatation chamber containing entrapped air causes the delivery system to float over the gastric contents. Gastric fluid enters through the apertures, dissolves the drug, and carries the dissolved drug for continuous transport across the intestine for absorption. Intragastric microballoons loaded with drug has been developed (Bv et al., 2008), in their outer polymer shells were prepared by novel emulsion solvent diffusion method. The ethanol: dichloromethane solution of drug and Eudragit-S were poured into an aqueous solution of PVA that was thermally controlled at 40°C. The gas phase generated in the dispersed polymer droplet by the evaporation of solvent forms an internal cavity in the microsphere of the polymer with the drug. The microballoons on floatation along with the surfactant, floated continuously for more than 12 h in the acidic medium in in-vitro conditions.

![Diagram of Intragastric floating gastrointestinal drug delivery device](image)

**Figure 2.13: Intragastric floating gastrointestinal drug delivery device**

*Inherent low-density systems*

It is highly desirable to develop DDS that float immediately following contact with gastric fluids. This can only be achieved if the low density of the device is provided from the beginning. Compared with systems initially settling down, the risk of premature emptying from the stomach is greatly reduced. Generally, inherent low density is provided by entrapment of air e.g., hollow chambers (Murphy et al., 2012) or by the additional incorporation of low-density materials, such as fatty substances or oils or foam powder (Streubel et al., 2002). Another single-unit, FDDS was developed with inherent low density, consisting of a hollow core (empty, hard gelatin capsule or polystyrene foam or pop rice grain) coated with two layers: a subcoat of cellulose acetate phthalate, and an outer drug-containing coating of EC/HPMC (Zhang et al., 2009). This type of system is very interesting for low-dose drugs but may not be suitable if larger amounts of drug are needed for an effective therapy. Multiple unit floating system has advantages as compare to single unit dosage forms. Multiple unit
floating systems reduces inter subject variability, increase patient compliance and it also lowers dose dumping (Sungthongjeen et al., 2008).

1. Floating microspheres: The methods for the preparation of microsphere typically are solvent evaporation or solvent diffusion method. Microspheres were prepared by using an emulsion-solvent diffusion method loaded with the ibuprofen in polymeric shells. (Kawahima et al., 1992). Multiple-unit floating microcapsules of atorvastatin calcium were developed to expand the gastric residence time of the drug, as ATC has maximum rate of absorption in the upper GI tract (Khan and Dehghan, 2012). The preparation procedure and mechanism of microballoon formation is schematically illustrated in Figure 2.14.

![Figure 2.14](image)

**Figure 2.14: Preparation procedure (emulsion-solvent diffusion method) and mechanism of microballoon formation.**

A solution of polymer and drug in ethanol/methylene chloride is poured into an agitated aqueous solution of polyvinyl alcohol. The ethanol rapidly partitions into the external aqueous phase and the polymer precipitates around the methylene chloride droplets. The subsequent evaporation of the entrapped methylene chloride leads to the formation of internal cavities within the microparticles. Simple

2. Floating beads: Low density floating beads were prepared for the preparation of multiple-unit FDDS. Bead type formulation containing air compartments was described (Bulgarelli et al., 2000). It is prepared by the emulsion gelation method (Talukdar and Fassihi, 2004). An aqueous solution of casein and gelatin was added to an outer mineral oil phase and stirred with a paddle stirrer. Foam was developed and stabilised by the
emulsifying properties of casein. The dispersed phase was solidified by cooling, leading to air bubble incorporation and the formation of large holes in the beads.

Beads of low methoxylated pectin and, optionally, sodium alginate crosslinked with calcium chloride were prepared (Talukder and Fassihi, 2004). The floating properties of the devices strongly depended on the subsequent drying process. Oven dried beads did not float, whereas freeze-dried beads remained floating for > 12 h in hydrochloride buffer pH 1.5 due to the presence of air-filled hollow spaces within the system.

**Effervescent systems**

1. Gas generating systems: These are matrix types of systems formulated in such a way that by contacting with the acidic gastric contents, it liberates carbon dioxide (CO₂) which gets entrapped in swollen hydrocolloids, and causes the formulation to float in the stomach. These buoyant systems are formulated with the help of swellable polymers such as polysaccharides e.g. methylcellulose and chitosan and various effervescent compounds, e.g., sodium bicarbonate, tartaric acid, and citric acid. Garg and Sharma (2003) reported an appropriate ratio of effervescent compounds citric acid and sodium bicarbonate is to be 0.76:1.

A new multiple type of floating dosage system composed of effervescent layers and swellable membrane layers coated on sustained release pills had been developed (Shah *et al.*, 2011). The inner layer of effervescent agents containing sodium bicarbonate and tartaric acid was divided into 2 sublayers to avoid direct contact between the 2 agents. These sublayers were surrounded by a swellable polymer membrane containing polyvinyl acetate and purified shellac. When this system was immersed in the buffer at 37°C, it settles down and the solution permeates into the effervescent layer through the outer swellable membrane. CO₂ is generated by the neutralization reaction between effervescent agents, producing swollen pills (like balloons) with a density less than 1.0 g/ml. It was found that the system had good floating ability independent of pH and
viscosity of the medium and the drug (para-amino benzoic acid) was released in a sustained manner.

Expandable, gastroretentive sustained-release formulation of carvedilol phosphate was developed that swell rapidly in an aqueous environment and thus reside in stomach over an extended period of time (Avachat et al., 2011). In addition to this, gas-forming agents were incorporated. As the gas formed, the density of the system was reduced and thus the system tended to float on the gastric contents.

Atyabi and coworkers (1996) developed a floating system using ion exchange resin that was loaded with bicarbonate by mixing the beads with 1 M sodium bicarbonate solution. The loaded beads were then surrounded by a semipermeable membrane to avoid sudden loss of CO$_2$. Upon coming in contact with gastric contents an exchange of chloride and bicarbonate ions took place that resulted in CO$_2$ generation thereby carrying beads toward the surface of gastric contents and producing a floating layer of resin beads as shown in Figure 2.15. The in-vivo behavior of the coated and uncoated beads was monitored using a single channel analyzing study in 12 healthy human volunteers by $\gamma$-radioscintrigraphy. Studies showed that the gastric residence time was prolonged considerably (24 h) compared with uncoated beads (1 to 3 h) (Arora et al., 2005).

Figure 2.15: Pictorial presentation of working of effervescent floating drug delivery system based on ion exchange resin (Arora et al., 2005)

Generally, effervescent systems suffer from the disadvantage of inability not to float immediately after swallowing because the process of gas generation takes some
time. Therefore, these could be cleared from the stomach before becoming effective. The performance of low-density, FDDS is strongly dependent on the filling state of the stomach. Nevertheless, this approach can successfully prolong the gastric retention time (Talukder and Fassihi, 2004) and has already led to the production of pharmaceutical products, which are commercially available on the market.

2. Volatile liquid containing systems: An inflatable chamber is incorporated which contains the liquid e.g. ether that gasifies at body temperature to cause the inflation of the chamber in the stomach which sustains the gastric retention time of the drug delivery system.

These gastro-inflatable DDS are osmotically controlled floating systems containing a hollow deformable unit that can convert from a collapsed to an expanded position, and returns to the collapsed position after an extended period. The device inflates, and the drug is continuously released from the reservoir into the gastric fluid (Kumar and Kaur, 2011).

3. Intragastric osmotically controlled DDS consists of an osmotic pressure-controlled drug delivery device and an inflatable floating support in a bioerodible capsule. When the device reaches the stomach, bioerodible capsule quickly disintegrates to release the DDS. The floating support is made up of a deformable hollow polymeric bag containing a liquid that gasifies at body temperature to inflate the bag. The osmotic pressure controlled drug delivery device consists of two compartments:

- A drug reservoir compartment
- An osmotically active compartment

The drug reservoir compartment is enclosed by a pressure-responsive collapsible bag, which is impermeable to vapors and liquids and has a drug delivery orifice. The osmotically active compartment contains an osmotically active salt and is enclosed within a semipermeable housing.
In stomach, the water in the gastric fluid is continuously absorbed through the semipermeable membrane into the osmotically active compartment to dissolve osmotically active salt. An osmotic pressure is thus created, which acts as a collapsible bag, and in turn forces the drug reservoir compartment to reduce its volume and activate the release of the drug solution formulation through the delivery orifice. The floating support is also made to contain a bioerodible plug that erodes after a predetermined time to deflate the support. The deflated DDS is then excreted from the stomach (Heller, 2009).

Any solute released in the stomach will empty together with fluids and the whole surface of small intestine will be available for absorption. This should particularly be useful when an absorption window exists in proximal small intestine. In addition, with the total GI transit duration is increased, a greater amount of drug may be delivered and thus the relative bioavailability will consequently be increased. For instance, a significant increase in bioavailability of furosemide has been obtained (42.9%) when administered as a floating dosage form, compared to the commercially available tablet (Lasix, 33.4%) and the enteric product.

An FDDS offers advantages for drugs such as weak bases, which dissolve better in acid environment and are poorly soluble at higher pH. In such cases, drug dissolution has less chance to be a limiting step of the release if formulated into FDDS. Apart from the above mentioned advantages, FDDS is particularly useful for drugs unstable in intestinal fluids (Khan and Dehghan, 2012) and those which may undergo abrupt changes in their pH-dependent solubility due to factors such as food, age and pathological conditions of the GI tract, e.g., the bioavailability of captopril is reduced due to degradation at higher pH condition (Nur and Zhang, 2000). The only problem of floating systems is that they require sufficiently high levels of fluid in the stomach for the DDS to float therein and work efficiently. However, this can be overcome by administrating the dosage form with a glass full of water (200-250 ml) with frequent meals (Moes, 1993) or by coating the dosage form with bioadhesive polymers, thereby enabling them to adhere to the mucous lining of the stomach wall.