CHAPTER-I

Introduction
The goal of any drug delivery system is to provide a therapeutic amount of drug to the proper site in the body in order to promptly achieve and thereby to maintain the desired concentration. Recently, several technical advancements have been made. They have resulted in the development of new techniques for drug delivery. These techniques are capable of controlling the rate of drug delivery, sustaining the duration of therapeutic activity, and/or targeting the delivery of drug to a tissue. These advancements have led to the development of several novel drug delivery systems that could revolutionize the method of medication and provide a number of therapeutic benefits and the ultimate aim of these systems is to achieve the extended duration of drug levels but the methods of achieving this and the clinical performance of the products can vary considerably (Yie, 1992).

Prolonged release or sustained release dosage forms have many advantages in safety and efficacy over immediate release drug product in that the frequency of dosing can be reduced, drug efficacy can be prolonged and intensity of adverse effects can be decreased. Many techniques are capable of controlling the rate of the drug delivery, sustaining the duration of therapeutic activity and/or targeting the delivery.

The USP/NF presently recognizes several types of modified release dosage form such as extended, delayed and targeted release dosage form. The drug release from these takes place by diffusion, dissolution, erosion, osmotic and ion exchange resins mechanism. The matrix materials used for this purpose were natural, synthetic and semi synthetic polymers.
The extended duration of drug levels can be achieved through sustained release formulation. The term “sustained release is known to have existed in the medical and pharmaceutical dosage form formulated to retard the release of a therapeutic agent such that its appearance in the systemic circulation is delayed and / or prolonged thereby plasma profile was sustained. So the onset of pharmacological action will meet therapeutic needs (Joseph et. al., 1998).

1.1 Sustained Release:

Sustained release systems are designed to achieve slow release of drug over an extended period of time after administration of single dose (Sefton et. al., 1984). If the system provides control and drug release by temporal or spatial nature or both in the body then it is said to be controlled release system. Control delivery attempts to sustain drug action at a predetermined rate by maintaining a relatively constant, effective drug level in the body (Grodzinsky et. al., 1990).

1.1.1 Potential advantages of sustained release dosage forms

The potential advantages of the use of the sustained- release systems are as follows:

1. Avoid patient’s compliance problems (Grundy et. al., 1997, Vyas et. al., 2002).

2. Use less total drug: (a) Minimize or eliminate local side effects, (b) Minimize or eliminate systemic side effects and (c) Minimize drug accumulation with chronic use.

3. Improved efficiency in treatment: (a) Cure or control condition more promptly, (b) Improve control of condition i.e., reduces fluctuation in drug levels and (c) Improve bioavailability of some drug.

4. Economy.
1.1.2 Techniques for preparing prolonged action dosage forms

Barrier coating, embedding in slowly erodible matrix, skeleton type preparation, repeat action preparation, ion - exchange resin beads, hydrophilic matrix (Jantzen et. al., 2002, Kydonieus., 1980).

1. Polymer resin beads
2. Passage – sponge formation
3. Chemical complexation

Among the different methods listed above, the barrier coating technique is the earliest mode to retard release and still applied to a large variety of drugs, controlling their release for sustained action.

1.2 Microencapsulation

Microencapsulation is a process in which tiny particles or droplets are surrounded by a coating to give small beads with many useful properties. In simple terms, a microcapsule is a small sphere with a uniform wall around it. The material inside the microcapsule is referred to as the core, internal phase, or fill, whereas the wall is sometimes called a shell, coating or membrane. Most microcapsules have diameters between a few micrometers and a few millimeters. A wide range of coat materials were viz., lipids, wax, crystal starch, modified starch, cellulose, phospholipids and other polymers etc (Baken et. al., 1976). Many microcapsules however bear little resemblance to these simple spheres. The core may be a crystal a jagged adsorbent particle, an emulsion, a suspension of solids or a suspension of smaller microcapsules. The microcapsule even may have multiple walls.
The uniqueness of microencapsulation is the smallness of the coated particles and their subsequent use and adaptation to a wide variety of dosage forms and product applications which therefore might not have been technically feasible. Because of the smallness of the particles, drug moieties can be widely distributed throughout the gastrointestinal tract, thus potentially improving drug absorption.

The first industrial product employing microencapsulation was carbonless copy paper developed by Green and Schleicher in the 1950s. To this day, carbonless copy paper is one of the most significant products to utilize microencapsulation technology and is still produced commercially. The technologies developed for carbonless copy paper have led to the development of various microcapsule products in recent years.

In general microcapsules have size from 5-500 µm; they can be made below 1 µm and up to 5000 µm in size. The microcapsules may be isolated as free flowing powders, collected as drug aggregates or suspended directly in a vehicle for administration. Microcapsule may assume various shapes such as globular, spheroidal, kidney like, rice grain like, flocculent and massive. The thickness of the wall is generally within a range from 0.2 µm to several micrometers, but normally the thickness exceeds 10 µm. Wall may have a single layer structure or multi layer structures. The capsule wall should be inert to the substance it contains, possess enough strength to allow for normal handling without rupture. The contents of the capsules are contained within the wall until released by some means that serve to break, crush, melt, dissolve rupture or remove the capsule shell or until the internal phase is caused to diffuse out through the capsule wall.
1.3 Natural Microcapsules:

Microorganisms offer certain advantages over conventional micro-encapsulation processes, as the microcapsules are preformed. The technology is based on using yeast and other single microorganisms as capsules to protect and deliver active compound. Microorganisms were first used to encapsulate only fat-soluble materials (Vyas et al., 2002). Dunlop has found that it is possible to encapsulate core material such as a dye into yeast with a more natural fat content (i.e. less than 40%). Its development team employed lipid-extending substances that are taken into the yeast cell. If a substance is soluble or freely dispersible within this lipid extending substance, then the yeast also absorbs the core material (Namdeo et al., 1999). The Dunlop work has been further refined by AD2, Birmingham, to such an extent that yeast containing low levels of fat (less than 10%) can now be used as microcapsules without so-called lipid extending substances.

The technology of microencapsulation using yeast cell is unique as it involves the use of preformed walls and membranes of microorganisms to provide the capsule. This method can improve the shelf life and bioavailability of active ingredients (Heller et al., 1980).

1.3.1 Characteristics of microcapsules:

Converting liquids to solids, providing environmental protection, improved material handling properties, colloidal and surface properties can be altered, control the release characteristics and masking or protecting the core material as well as decreasing the volatility (Jameela et al., 1995, Pitt., 1992).
1.3.2 *The following characteristics of microcapsules do interest the researchers:*

a) **Size and size distribution** - low size increases the mechanical strength and also ease of application.

b) **Loading fraction** - This is the weight ratio of core to wall of the microcapsule, the higher in this ratio the better is the production efficiency but poorer would be the stability.

c) **Release properties** - Rate of release from microcapsules depends largely on the structure of the polymer wall, which in turn is influenced by the conditions employed in the preparation. Wall characteristics like crystallinity, cross-link density and porosity play big role in determining the release rate. As the crystallinity and cross-link density of the wall increases, the release rate reduces substantially. The other important factor is the outside environment; if it is of the same type as that of the core material, the rate of release will be high. The core ingredient may be released by: i) Mechanical stimulus, ii) Chemical stimulus, or iii) Thermal stimulus. The resultant release rate can normally be expressed as a first order rate process, i.e., \(-dc/dt = kc\), where \(k\) is the diffusion constant and \(c\) is the concentration gradient (Pitt., 1992 and Pitt *et al.*, 1999).

d) **Thermal stability** - it is very important when field of application is at a high temperature.
1.4 Anti Viral Drugs:

Antiviral drugs are a class of medication used specifically for treating viral infections. Like antibiotics, specific antiviral are used for specific viruses. Antiviral drugs are one class of anti-microbial, a larger group which includes antibiotics, antifungal and anti-parasitic drugs. They are relatively harmless to the host and therefore can be used to treat infections. Most of the antivirals now available are designed to help deal with HIV, herpes virus, which is best known for causing cold sores but actually covers a wide range of diseases, and the hepatitis B and C viruses, which can cause liver cancer. Researchers are now working to extend the range of antiviral to other families of pathogens (Sriram et al., 2003, Abu et al., 2000).

The emergence of antivirals is the product of a greatly expanded knowledge of the genetic and molecular function of organisms, allowing biomedical researchers to understand the structure and function of viruses, major advances in the techniques for finding new drugs and the intense pressure placed on the medical profession to deal with the deadly virus. Eleven drugs approved by the Food and Drug Administration for the treatment of viral infections (other than those caused by human immunodeficiency virus). They are seven nucleoside analogues, two closely related 10- carbon ring amines, one pyrophosphate analogue, and a recombinant protein produced in bacteria. Of the five antiviral drugs namely Valacyclovir, ganciclovir, penciclovir, famciclovir and acyclovir, in the present study acyclovir was employed.

1.4.1 Valacyclovir:

Valacyclovir, the L–valyl ester of acyclovir, is available only as an oral formulation. After ingestion, the drug is rapidly converted to acyclovir by the enzyme valacyclovir hydrolase in the gastrointestinal tract and liver. Its oral bioavailability is
three to five times that of acyclovir. Valacyclovir has proved effective in the treatment of infections caused by herpes simplex virus and *Varicella zoster* virus and as prophylaxis against cytomegalovirus disease. Valacyclovir is administered orally, 1000 mg twice daily, for suppressive therapy for HIV infected persons, 500mg twice daily. The product is more expensive and larger tablets. Mainly used for genital herpes and the dosage is up to sixteen weeks.

1.4.2 Ganciclovir:

Ganciclovir differs from acyclovir by the addition of a hydroxymethyl group at 3′ position of the acyclic side chain. Its metabolism and mechanism of actions are similar to those of acyclovir, except that it has a 3 carbon with a hydroxyl group that can permit primer-template extension and so is not an absolute DNA chain terminator. Ganciclovir is converted to ganciclovir monophosphate by a viral encoded phosphotransferase produced in cells infected with cytomegalovirus. Intravenous ganciclovir is effective for the suppression and treatment of cytomegalovirus diseases (Jaime *et al.*, 1998). Oral ganciclovir has also proved useful for the suppression of cytomegalovirus disease but its value is limited by its low bioavailability (Joel *et al.*, 2001).

1.4.3 Penciclovir:

Penciclovir is structurally similar to ganciclovir differing only by the substitution of a methylene bridge for the ether oxygen in the acyclic ribose part of the molecule. Its metabolism and mechanism of action are similar to those of acyclovir, except that it is not an obligate DNA- Chain terminator. The in vitro inhibitory effects of penciclovir on herpes simplex virus types 1 and 2 and varicella-
zoster virus are similar to those of acyclovir. The oral bioavailability of it is very poor and has got a very high first pass effect, metabolized rapidly. It is available as a topical formulation for the treatment of herpes labializes (Jaime et. al., 1998, Joel et. al., 2001).

1.4.4 Famiclovir:
Famiclovir is the diacetyl 6 deoxy analogue of penciclovir. It is well absorbed after oral administration and is rapidly metabolized to penciclovir by deacetylation in the gastrointestinal tract, blood and liver after which it is oxidized by the liver at position 6 of the purine ring. The intracellular half life of the active drug, penciclovir triphosphate is very long, suggesting the potential for once daily dosing. Famiclovir is effective against genital herpes and herpes zoster infections (Jaime et. al., 1998, Joel et.al., 2001). 250 mg tablets are given orally thrice a day and for suppression therapy for HIV infected persons it is administered as 500 mg tablets twice a day up to four months. Famiclovir is mainly used for genital and labial herpes. It is available as smaller tablets but more expensive. The main disadvantage was complaints like nausea, diarrhea and severe headache during clinical trials.

1.4.5 Acyclovir:
Acyclovir is an analogue of 2’ deoxy Guanosine that exerts its antiviral effect after being metabolized to acyclovir triphosphate. Acyclovir triphosphate is 30 to 50 times as potent as an inhibitor of Herpes Simplex type 1 DNA polymerase. Acyclovir has proved effective for the treatment of infections caused by herpes simplex virus type 1 and 2 and varicella-zoster virus and for the suppression of some forms of cytomegalovirus disease (Jaime et. al., 1998, Joel et.al., 2001).
Acyclovir is an antiviral drug used for the treatment of herpes simplex virus and varicella zoster virus infections, including genital herpes simplex (treatment and prophylaxis), labial herpes simplex (cold sores), herpes zoster (shingles), acute chickenpox, herpes simplex encephalitis, acute mucocutaneous HSV infection in immuno compromised patients and herpes simplex keratitis. Acyclovir is currently marketed as capsules (200 mg), tablets (200, 400 and 800 mg) and suspension for oral administration, intravenous injection and topical ointment. Oral acyclovir is mostly used as 200 mg tablets, five times a day. In addition, long term administration of acyclovir (6 month or longer) is required in immunocompromised patients with relapsing herpes simplex infection. For neonatal HSV infections acyclovir is given orally as 60mg/kg per day in three divided doses and the duration is for 21 days.

India is a developing country and we can afford only cheaper and safe drugs especially in the case of the types of infections listed above. Acyclovir is considered as a first line agent for HSV – 1 and HSV – 2 infections.

Acyclovir absorption takes place passively in the stomach and actively in the upper portion of small intestine. In the form of microcapsules acyclovir would release the drug there in a controlled and prolonged manner so that the drug could be supplied continuously at the absorption site. Prolonged gastric retention improves bioavailability, reduces gastric waste and improves the solubility of the drug that are less soluble in a high pH environment. It is suitable for local drug delivery to the stomach and proximal small intestine. Initial loading dose helps to provide a better bioavailability of the drug with suitable therapeutic activity at the stomach and the mucoadhesive yeast microcapsules (sustenance dose) attach themselves to the villi of the small intestine and release the drug slowly to suite the active absorption hence to
provide substantial benefits for patients. Acyclovir is soluble in acidic pH and predominantly absorbed from the upper gastro intestinal tract. The favoured site for active uptake is Payer’s patches or lymphoepithelial M cell in the small intestine. I have targeted acyclovir microcapsules to the small intestine. It is a safe drug and generally well tolerated orally. It is clear that from above all the antiviral agents, acyclovir is the drug of choice since it has got a better patient compliance, better duration of action, safe drug, and lesser side effects, cheap and mainly used for various viral infections.

Valacyclovir, Penciclovir and Famiclovir are mainly used for genital and labial herpes infection. So citing the above reasons I chose acyclovir as the drug of choice for my work to formulate microcapsule using natural, bio-degradable and non-biodegradable polymers.

1.5 Pharmaceutical Suspension

A pharmaceutical suspension may be defined as a coarse dispersion containing finely divided insoluble material suspended in a liquid medium. The physical chemist defines the word “suspension” as two-phase system consisting of an undisclosed or immiscible material dispersed in a vehicle (solid, liquid, or gas).

Generally pharmaceutical suspensions contain aqueous dispersion phase however in some cases they may be an oily or organic phase. The suspensions have dispersed particles above the colloidal size that is mean particle diameter above 1µm and is maintained uniformly throughout the suspending vehicle with aid of single or combination of suspending agent.
Properties of Suspensions

- Suspensions should possess good pourability leading to ease of removal of dose from container.
- They should have good organoleptic properties.
- The particle size distribution should be uniform.
- There should be ease of redispersion of settled solid particles.
- They should be physically and chemically stable.
- They should be resistant against microbial contamination.

Classification

Based On General Classes
- Oral suspension
- Externally applied suspension
- Parenteral suspension

Based On Proportion of Solid Particles
- Dilute suspension (2 to 10% w/v solid)
- Concentrated suspension (50% w/v solid)

Based On Electro kinetic nature Of Solid Particles
- Flocculated suspension
- Deflocculated suspension

Based On Size of Solid Particles
- Colloidal suspension (< 1 micron)
- Coarse suspension (>1 micron)
- Nano suspension (10 nm)
Advantages and Disadvantages

- **Advantages**
  - Suspension can improve chemical stability of certain drug.
  - Drug in suspension exhibits higher rate of bioavailability than other dosage forms.
    Bioavailability is in following order,
    - Solution > Suspension > Capsule > Compressed Tablet > Coated tablet
  - Duration and onset of action can be controlled.
  - Suspension can mask the unpleasant/bitter taste of drug.

- **Disadvantages**
  - Physical stability, sedimentation and compaction can cause problems.
  - It is bulky and sufficient care must be taken during handling and transport.
  - It is difficult to formulate.
  - Uniform and accurate dose cannot be achieved unless suspensions are packed in unit dosage form.

**Quality control tests for suspensions**

- **Sedimentation volume:**
  Redispersibility is the major consideration in assessing the acceptability of a suspension. The measurement of the sedimentation volume and its ease of redispersion, form two of the most common basic evaluative procedures. The sedimentation volume is the simple ratio of the height of sediment to initial height of the initial suspension. The larger the value better is the suspend ability.

- **Particle size and size distribution:**
The freeze-thaw cycling technique used to assess suspension for stress testing for stability testing result in increase of particle growth and may indicate future state after long storage. It is of importance to study the changes for absolute particle size and particle size distribution. It is performed by optical microscopy, sedimentation by using Andreasen apparatus and Coulter counter apparatus. None of these methods are direct methods. However microscopic method allows the observer to view the actual particles. The sedimentation method yields a particle size relative to the rate at which particles settle through a suspending medium.

- Rheological studies:

  Rheological methods can help in determining the settling behavior of the suspension. Brookfield viscometer with variable shear stress control can be used for evaluating viscosity of suspensions. It consist of T-bar spindle which is lowered into the suspension and the dial reading is noted which is a measure of resistance the spindle meets at various levels in the suspension. This technique also indicates in which level of the suspension the structure is greater due to particles aggregates. Data obtained on aged and stored suspension reveals whether changes have taken place.

- Stability testing:

  It is not possible to conduct accelerated temperature studies as it can be done in solutions. The formulation exhibiting thixotropic properties a rise in temperature would change the properties. In this physical form, the preparation would exhibit parameters that could not be extrapolated to those that would exist in the normal system. The valid temperature data could be obtained that will be useful in the estimation of the physical stability of a product at normal storage conditions. The
extended aging tests must be employed under various conditions to obtain the desired information.

**Formulation Additives**

In addition to vehicle, stabilizer, sweetening and flavouring agents, which are common in liquid dosage forms, the following additives are required to prepare suspensions which include:

1. **Suspending and Thickening agents:**

   They are added with the objective to increase apparent viscosity of the continuous, phase thus preventing rapid sedimentation of the dispersed particles. The selection of the type and concentration of a suspending agent depends on sedimentation rate of dispersed particles, pourability and spreadibility. The ideal suspending agent should have a high viscosity at negligible shear i.e., during shelf storage and it should have a low viscosity at high shearing rates i.e., it should be free flowing during agitation, pouring and spreadibility. A suspending agent that is thixotropic as well as pseudoplastic should prove to be useful as it forms a gel on standing and becomes fluid when shaken. They include natural polysaccharides (Gum Acacia, Gum Tragacanth, Guar Gum, Sodium Alginate, Xanthan Gum and Carrageenan), Semi-synthetic polysaccharides (Sodium Carboxymethylcellulose, carboxy methyl cellulose (CMC), Methyl Cellulose, Hydroxyethyl Cellulose, Hydroxypropyl Cellulose, Hydroxypropyl Methyl Cellulose and Microcrystalline Cellulose), Clays (Aluminium Magnesium Silicate, Bentonite and Hectorite) and synthetic agents (Carbomer, Colloidal silicon dioxide). Pseudoplastic substances like tragacanth, sodium alginate and sodium carboxymethyl cellulose show these desirable
qualities. In cases of combination use of suspending agents like bentonite and CMC dispersions are both pseudo plastic and thixotropic.

2. **Wetting agents:**

   Although some insoluble solids get easily gets wet by water, most of them exhibits hydrophobicity and does not get easily wetted by it. Wetting agents are additives which are usually added to decrease this hydrophobicity. These agents generally get adsorbed at the solid-liquid interface and promote wetting of the solid particles by the liquid of the dispersion medium. Eg: surfactants, hydrophilic polymers, hydrophilic liquids.

3. **Dispersing agents:**

   These additives are generally added as an aid to uniform distribution and dispersion of solid particles of the dispersed phase. Such agents are generally used during the preparation of deflocculated suspensions where they get adsorbed at the solid-liquid interface. Wetting agents such as surfactants are often employed as dispersing agents. Other agents used for this purpose include agents such as Darvans, Daxads, etc. which carry a good surface charge and get absorbed on the particles of the dispersed phase thus preventing their agglomeration.

4. **Flocculating agents:**

   These are substances added to cause controlled aggregation of the particles of the dispersed phase in a suspension. Examples of such agents include surfactants, electrolytes and hydrophilic polymers.

**Applications**

- Suspension is usually applicable for drug which is insoluble or poorly soluble.
- To prevent degradation of drug or to improve stability of drug.
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- To mask the taste of bitter of unpleasant drug.
- Suspension of drug can be formulated for topical application.
- Suspension can be formulated for parenteral application in order to control rate of drug absorption.
- Vaccines as an immunizing agent are often formulated as suspension.

Storage Requirements (Labelling)
- Shake well before use
- Do not freeze
- Protect from direct light (For light sensitive drugs)

Objective of the work:

Several dosage forms have been developed and reported in literature for sustained release of various bioactive materials of which microcapsules and microparticles are one among them. Advantages associated with such dosage forms include high drug loading, simple and cost effective manufacturing process, the availability of wider range of polymers and excipients for sustaining the drug release.

Acyclovir is a white, crystalline powder with the molecular formula C_{8}H_{11}N_{5}O_{3} and a molecular weight of 225. The maximum solubility in water at 37°C is 2.5 mg/mL. The p^ka values of acyclovir are 2.27 and 9.25. The pharmacokinetics of acyclovir after oral administration have been evaluated in healthy volunteers and in immunocompromised patients with herpes simplex or varicella-zoster virus infection. Acyclovir pharmacokinetic parameters are summarized in table 1.
Table: 1 Acyclovir Pharmacokinetic Characteristics (Range)

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Range</th>
</tr>
</thead>
<tbody>
<tr>
<td>Plasma protein binding</td>
<td>9% to 33%</td>
</tr>
<tr>
<td>Plasma elimination half-life</td>
<td>2.5 to 3.3 hr</td>
</tr>
<tr>
<td>Average oral bioavailability</td>
<td>10% to 20%*</td>
</tr>
</tbody>
</table>

*Bioavailability decreases with increasing dose.

In one multiple-dose, crossover study in healthy subjects (n = 23), it was shown that increases in plasma acyclovir concentrations were less than dose proportional with increasing dose, as shown in table 2. The decrease in bioavailability is a function of the dose and not the dosage form.

Table: 2 Acyclovir Peak and Trough Concentrations at Steady State

<table>
<thead>
<tr>
<th>Parameter</th>
<th>200 mg</th>
<th>400 mg</th>
<th>800 mg</th>
</tr>
</thead>
<tbody>
<tr>
<td>$C_{ss \text{ max}}$</td>
<td>0.83 mcg/mL</td>
<td>1.21 mcg/mL</td>
<td>1.61 mcg/mL</td>
</tr>
<tr>
<td>$C_{ss \text{ trough}}$</td>
<td>0.46 mcg/mL</td>
<td>0.63 mcg/mL</td>
<td>0.83 mcg/mL</td>
</tr>
</tbody>
</table>

The presently available conventional therapy is associated with a number of drawbacks such as highly variable absorption and low bioavailability (10–20%) after oral administration. Furthermore, with increase in dose, there was decrease in bioavailability. Moreover, because the mean plasma half life of the drug is 2.5 h, five times a day administration is required. In order to make oral therapy of acyclovir
more patients compliant and to overcome the drawbacks of such therapy, there is need to develop controlled drug delivery dosage form.

Acyclovir formulations are available in the form of injections, oral suspensions etc. It is clear from the dosing & frequency is very high and frequency is also 4-5 times per day orally. So in the present thesis work, we aim to formulate a sustained action dosage form of acyclovir in the form of microcapsules using biodegradable and non-biodegradable and a natural microbial carrier. *Saccharomyces cerevisiae* a natural microbial carrier and other polymers are guar gum, egg albumin and ethyl cellulose.

*Saccharomyces cerevisiae* or baker’s yeast is used in the fermentation of beer and wine and in baking. *Saccharomyces cerevisiae* is yeast of great economic importance, the cells of which are elliptical 6-8 by 5μm. Yeast and molds can tolerate more acidic conditions than most other microbes. The technology of microencapsulation using yeast cell is unique as it involves the use of preformed walls and membranes of microorganisms to provide the capsule. This method can improve the shelf life and bioavailability of active ingredients.

**Novelty of the work:**

1) Since the plasma protein binding of the drug acyclovir is between 9% to 33% which is very low, so there is a need of sustaining the drug for a longer time to achieve a therapeutic concentration and to avoid multiple dosing, and this has been done by preparing a sustained formulation in the form of microcapsules of acyclovir which helps in the slow release of the drug.
2) The average oral bioavailability of acyclovir is 10 to 20% and the bioavailability decreases with increasing the dosage, since it is actively absorbed from the small intestine. Its bioavailability can be improved if the formulation stays in the intestine for a longer duration and able to release the drug once the active absorption sites are available again.

3) *Saccharomyces cerevisiae* or baker’s yeast has been used as an encapsulating agent for the encapsulation of flavoring agents and pesticides. (Bishop *et al.*, 1998). No work has been previously done to encapsulate a drug using *Saccharomyces cerevisiae*. It involves preformed walls and membrane of the microorganism to provide a capsule like shell. The *Saccharomyces cerevisiae* has to be pre-treated with sodium azide a respiratory inhibitor used to prevent the cells from performing any energy dependant process. Sterilization by autoclaving is a thermally destructive process denaturing any carrier protein molecules likely to be involved in facilitated diffusion process. The pre treated dead yeast cells with intact cell membrane were used for the encapsulation of acyclovir. *Saccharomyces cerevisiae* has got an excellent muco-adhesive property, so thereby can release the drug slowly and in a constant manner.

4) Other polymers selected were guar gum, egg albumin and ethyl cellulose to formulate microcapsules of acyclovir. Guar gum and egg albumin also have a good mucoadhesive property. Ethyl cellulose forms good films and is also used for sustained action preparations. These polymers were used to formulate microcapsules of acyclovir as they intensify the contact between the microcapsules and the site of
absorption thereby reducing the luminal diffusion pathway of the drug and this leads to significant improvement of the drug deliver to the site.

Thus the above observation prompted us to formulate and evaluate microparticles of acyclovir, for improving the pharmacological effect, avoiding the side effects, improving patient compliance, increasing the duration of action and increasing the bioavailability. Different batches of acyclovir microcapsules were prepared using different ratios of encapsulating agent (Saccharomyces cerevisiae or baker’s yeast, guar gum, egg albumin and ethyl cellulose) and drug at different temperature and stirring rate. The microcapsules were then studied for particle size analysis, entrapment efficiency, drug-polymer compatibility, differential scanning calorimetry, surface morphology and stability studies. In-vitro drug release studies were also studied. Further, kinetic modellings were employed to find out release mechanisms.

To select the ideal microcapsules made from the above polymers or microencapsulating agent in terms of drug content, drug release and stability.

To formulate a dosage form like suspension with the ideal microcapsules along with loading dose and compare the formulation with marketed acyclovir formulation. The prepared dosage form was further characterized by physicochemical characters, particle size analysis, wt/ml, drug content, in-vitro study, rheological study, sedimentation volume and stability study.
The following procedures were followed:

1) To prepare and characterize micro particles of acyclovir using biodegradable and non biodegradable encapsulating agents.

2) To evaluate the feasibility of micro-particles of acyclovir in terms of entrapment efficiency and to compare them with that of a marketed product.

3) To evaluate the micro particles as carriers in the form of suspension and to evaluate the feasibility of the formulation and to evaluate the various characteristic features and to compare them with that of a marketed product.

4) To determine pharmacokinetic parameters of some selected formulations.