CHAPTER-1
INTRODUCTION

1.1. NOVEL DRUG DELIVERY SYSTEM

During the past decade, a new era of science and technology has emerged in pharmaceutical research aimed towards the development of advanced drug delivery systems. For new drug delivery systems, normal concerns exist in areas of cost-efficient treatment, patient compliance and optimum drug delivery and bioavailability. Today the landscape of novel drug delivery technologies has become highly competitive and rewarding. This field represents one of the major research and development focus areas of pharmaceutical field in view of increasing awareness about patents, globalization, constraints in new drug discovery as well as potential, fortified with therapeutic benefits for the consumer. The method by which a drug is delivered can have a significant effect on its efficacy. To reduce drug decomposition and loss, to prevent side-effects and to increase bioavailability and the drug availability in the target zone, various dosage forms and drug targeting system are presently under development.

Novel Drug Delivery systems have seen a foray of transformations right from microencapsulation, transdermal delivery, liposomal vesicles, nanoparticles and latest being use of extracellular matrices. The 1950s were the initial stages where the focus was on microencapsulated drug particles. These drug particles were packed in tiny shells or capsules of dimensions measurable in micrometers and delivered throughout the body. A major facelift was brought about with the use of polymers for the manufacture of capsules or cages in 1960. Besides adding to the flexibility and versatility of the process of drug delivery, a few concerns over the pulsatile nature of drug delivery were also mitigated. The advent of transepithelial transdermal delivery strategies in 1990s had added to multi-dimension nature of NDDS. The subsequent addition of liposome at the commencement of this decade has added to the repertoire of existing drug delivery systems. Several strategies are being tried out currently to discover novel carriers for the drug to be delivered specifically and effectively.
1.1.1. **Advantages of Novel Drug Delivery Systems**

- The targeted delivery of the drug to the requisite site of action regulates the concentration of the drug in the blood stream, thus preventing the fluctuation of the drug concentration in the blood stream. This is especially critical for drugs with a narrow therapeutic index.
- Novel drug delivery systems control the release of the drug within the body which could open up avenues towards controlled chemical action against maladies like tumors.
- The drug loading into the carrier can be optimized, which is essentially a measure against invoking an undesirable immunological response within the body as well as prevent any toxicity due to the drug or the carrier system.
- Novel drug delivery systems provide protection to the drug from annihilating factors such as degradative enzymes like proteases, suboptimal pH conditions and immunologic agents.
- Externally, the patients find the process less cumbersome and the regime easy to abide.
- The reduced immunogenicity of the delivery systems decreases the complications associated with the induction of the drug into the body.
1.2. **ORAL CONTROLLED DRUG DELIVERY SYSTEM**

Oral drug delivery has been considered as the most widely used route among all the other routes that have been utilized for systemic delivery of drug in various pharmaceutical dosage forms. The main reasons for the popularity of oral route may be attributed to its ease of administration. Oral sustained drug delivery system is complicated by limited gastric residence time. Rapid GI transit can prevent the complete drug release in the absorption zone and reduce the efficacy of the administered dose, since most of drugs are absorbed in stomach or upper part of the small intestine. To overcome the above problems, various approaches have been studied to increase gastric residence of drug delivery systems in the upper part of the gastrointestinal tract including floating drug dosage systems, modified shape systems, swelling or expanding systems, high density systems, mucoadhesive systems and other delayed gastric emptying devices. Advances in oral controlled-release technology are attributed to the development of new biocompatible polymers and machineries that allow preparation of novel design dosage forms in a reproducible manner.

Controlled drug delivery take place when a polymer, whether it is a natural or synthetic, is combined with a drug or other therapeutic agent in such a way that the drug is released from the product in a predesigned fashion. The release of the drug may be constant over a long term. It may be cyclic over a long term or it may be stimulated by the environment or other external circumstances. Providing control over the drug release may be the most important factor when traditional oral or injectable formulations cannot be used. These include circumstances requiring the slow release of water-soluble drugs, the rapid release of low-solubility drugs, drug delivery to target sites, delivery using particulate systems, delivery of two or more therapeutic agents in the same formulation and approach based on vehicle that can dissolve or degrade and be readily removed.

An ideal drug delivery dosage form should be

- Inert
- Biocompatible
- Mechanically strong
- Comfortable to the patient
- Capable of achieving high drug loading
- Safe from accidental release
- Simple to administer and remove
- Easy to fabricate and sterilize.

The prime objective in designing a controlled release drug delivery system is to deliver the drug at a rate required to achieve and maintain a constant drug blood level. This implies that the rate of delivery from the dosage form must be independent of the amount of drug remaining in the dosage form and constant over time\textsuperscript{14}. Sustained release, controlled release, timed release, sustained action, extended action, prolonged action, depot and repository dosage forms are terms used to name drug delivery systems that are designed to attain a prolonged therapeutic effect by continuously releasing the drug over an extended period of time after administration of single dose\textsuperscript{15}.

The conventional tablet or capsule provides only a single and transient burst of drug. Problems occur when the therapeutic range is very narrow or when the peak is greater than the upper limit of this range. Controlled release drug delivery systems improve the safety and minimize side effects of the drug by reducing the drug fluctuation level in the blood. Prolonged release dosage forms also minimize the drug fluctuation levels in plasma by slowing down the absorption rate by slowing drug release rate\textsuperscript{16}. 
1.2.1. Advantages of Controlled Release Dosage Forms

- Improves the patient compliance due to reduction in the frequency of dosage administration\textsuperscript{17}.
- Employ minimum drug
- Minimize or eliminate the local and systemic side effects
- Reduce drug accumulation with the chronic dosing
- Improves therapeutic efficacy
- Cure or control conditions more promptly
- Reduce the fluctuation in drug blood level
- Improve or enhance the bioavailability of certain drugs
- Make use of special release effects, e.g. Sustained release aspect for morning relief of arthritis by dosing before bed time.

1.2.2. Disadvantages of Controlled Release Dosage Forms

- Unpredictable and poor \textit{in-vitro, in-vivo} correlations, dose dumping, reduced potential for dosage adjustment
- Poor systemic availability
- Effective drug release is limited by GI residence time
1.3. MICROENCAPSULATION

Microencapsulation is a process whereby small discrete solid particles or tiny liquid droplets are surrounded and enclosed by an intact shell\textsuperscript{18}. Microencapsulation is a means of applying relatively thin coatings to small particles of solids or droplets of liquids and dispersions. Coating of particles ranging dimensionally from several tenths of micron to 5000 microns in size. Microencapsulation provides the means of converting liquid to solids, altering surface and colloidal properties, providing environmental protection of drug and controlling drug release characteristics or availability of coated polymers. 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. Because of the smallness of the size, drug particles can be widely distributed throughout the gastrointestinal tract, thus potentially enhancing drug absorption.

The first research leading towards the development of microencapsulation procedures for the Pharmaceuticals was published by Bungenburg de Jong and Kan in 1931 and dealt with the preparation of gelatin spheres by coacervation process. Microcapsules continue to be much interest in controlled release based partly on relative ease of design and formulation and partly on the advantages of micro particulate delivery systems.

1.3.1. Reasons for Microencapsulation

- The core must be protected from its surroundings, as in isolating vitamins from the deteriorating effects of oxygen, retarding evaporation of a volatile core, improving the handling properties of a sticky material or isolating a reactive core from chemical attack.
- To control the release rate at which it leaves the microparticles, as in the sustained or controlled release of drugs.
- To mask the bitter taste or odor of the core material\textsuperscript{19}.  

\textsuperscript{19}
1.3.2. Ideal Characteristics of Drug for Microencapsulation

- The drug should not be adversely affected by the process.
- No stability problem
  Drugs which are not stable in GI tract cannot be administered as oral controlled release dosage forms. e.g. Nitroglycerine.
- There should be no harmful effect associated with the final product.
- Therapeutic range
  A drug for controlled delivery system must have a wide therapeutic range.
- Therapeutic index of drug
  The ratio of maximum safe concentration to the minimum effective concentration of drug is called as therapeutic index. The drugs with narrow therapeutic index have toxic concentration nearer to their therapeutic range.
- Drugs whose pharmacologic effect is independent of its concentration are poor candidates for sustained or controlled release systems.
- Elimination half life
  Smaller the half life, more the amount of active medicament to be used in the controlled release dosage form\(^2\). Drugs with half life between 2 to 4 h are ideal candidates for sustained or controlled release systems e.g. Propranolol.

1.3.3. Advantages of Microencapsulation

- Microencapsulation provides delivery of drug to the target site with specificity, if modified, and maintain the desired concentration at the site of interest without untoward side effects.
- Solid biodegradable microparticles have the potential throughout the particle matrix for the controlled release of drug.
- Microparticles received much awareness not only for the prolonged release, but also for targeting of Anti-cancer drug to the tumor.
- Studies on the macrophage uptake of microparticles have shown their potential in targeting drugs to pathogens residing intra-cellularly\(^1\).
1.3.4. Applications of Microencapsulation

- The microencapsulated drug can be compressed as tablets or filled in capsules or administered as parenteral dosage forms\textsuperscript{21}.
- Microencapsulation method is used to prepare enteric-coated dosage forms, so that the drug will be absorbed selectively throughout the intestine than stomach.
- Bitter taste of several drugs can be masked by microencapsulation method.
- Microencapsulation method has been used to improve the flow property of certain vitamins. For example, the non-flowable solid mixture of Riboflavin, Niacin, Thiamine and Iron phosphate may be encapsulated to improve the flow property.
- Microencapsulation provides environmental protection of drugs from humidity, light, oxygen or heat.
- The separation of incompatible drugs can be achieved by microencapsulation. For example, the stability enhancement of incompatible Aspirin-Chlorpheniramine maleate mixture was accomplished by microencapsulating both of them before mixing.
- Microencapsulation can be used to reduce the volatility of certain drugs. An encapsulated volatile material can be stored for longer period without substantial evaporation.
- Microencapsulation has been used to reduce the potential danger of toxic or noxious substances. The toxicity occurs due to handling of herbicides, fumigants, pesticides and insecticides have been decreased by microencapsulation process.
- The hygroscopic character of many core materials can be reduced by microencapsulation.
- Many drugs were microencapsulated to reduce gastric irritation.
1.3.5. Microparticles

Microparticles are of two types:

- **Microcapsules**: The entrapped material is completely enclosed by a distinct capsule wall.
- **Microspheres**: The entrapped material is distributed throughout the entire microsphere matrix.

![Microcapsule and Microsphere](image)

**Figure- 1: Microcapsule and Microsphere**

The coating material can be selected from a wide variety of natural and synthetic polymers, depending upon the material to be coated and the characteristics desired. Microparticle carrier systems made from the naturally-occurring biodegradable polymers have made considerable notice for several years in sustained or controlled drug delivery. However, the success of these microparticles is limited by the short residence time of the drug on the absorption site. Therefore, it would be advantageous to have means of providing an intimate contact of the drug delivery system with the absorbing membranes. This can be achieved by coupling bio/muco-adhesion characteristics to microspheres/microcapsules and developing bio/muco-adhesive microparticles.
1.3.6. MICROENCAPSULATION FOR NSAIDS

NSAIDs are among the most commonly prescribed medications in the world. The use of non-steroidal anti-inflammatory drugs (NSAIDs) began over 100 years ago with the introduction of Salicylic acid for the treatment of rheumatic diseases. Almost all the NSAIDs available at the market have severe side effects. The gastrointestinal tract (GIT) is the main target of NSAID toxicity. It is the most frequent organ affected by adverse drug reactions and unfortunately, it is the most common drug-induced toxicity that can be fatal. World over, more than 35 million people consume these drugs on a daily basis and about 30% of users may develop GIT toxicity of sufficient degree requiring a physician’s intervention\textsuperscript{22,23}.

Most of the conventional NSAIDs have a shorter half-life which requires frequent dosing and thus reduces the patient compliance. As awareness of the gastrointestinal side effects related with NSAIDs increases, safety becomes a major necessity in treatment. A trend in development of NSAID has been attempted to improve therapeutic efficacy and reduce the gastrointestinal side effects through altering dosage forms by modifying the release of formulations to optimize drug delivery. One such approach is using polymeric microparticles as drug carriers. These formulations are designed to increase patient compliance through a prolonged effect and reduce adverse effects through lowered peak plasma concentration.

1.3.7. Advantages of NSAIDs Microencapsulation

- Microencapsulation provides constant and prolonged therapeutic effects, which will reduce the dosing frequency and thereby improving patient compliance.
- Effective drug utilization will improve the absorption and bioavailability of drug and reduce the intensity of adverse effects.
- Microspheres morphology allows a controllable variability in drug release.
Multipariculate delivery systems spread out more uniformly in the gastrointestinal tract.

Unwanted retention of polymeric material with matrix tablets on chronic dosing can also be avoided.

1.4. MUCOADHESIVE DRUG DELIVERY SYSTEM

Various approaches have been attempted to prolong the residence time of the dosage forms at the absorption site. One such attempt is the development of oral controlled or sustained release bio/mucoadhesive system. In 1980, Professor Joseph. R. Robinson developed the concept of bioadhesion as a new approach to prolong the residence time of several drugs on the ocular surface\(^24\). Later several gastrointestinal bio/muco adhesive dosage forms such as microspheres, discs and tablets have been developed and reported by various research groups\(^25\).

Mucoadhesive systems are drug delivery systems, which utilize the property of bio/mucoadhesion of certain polymers, which become adhesive on hydration and hence can be used for targeting a drug to a particular region in the body for extended periods of time.

Adhesion can be defined as the bond produced by contact between a pressure-sensitive adhesive and a surface\(^26\). The American Society of Testing and Materials have defined adhesion as the state in which two surfaces are hold together by interfacial forces, which also consist of valence forces, interlocking action, or both\(^27\).

A bioadhesive is defined as a substance that is capable of interacting with biological materials and being retained on them or holding them together for extended periods of time by interfacial forces. When the biologic surface is the mucosal tissue it is called mucoadhesive.
1.4.1. Advantages of Mucoadhesive Drug Delivery Systems

- The mucoadhesive systems are readily localized at the region applied, to improve and enhance the bioavailability of drugs. Greater bioavailability of Testosterone and its esters, Vasopressin, Dopamine, Insulin and Gentamycin was observed from mucoadhesive dosage systems\(^{28,29}\).

- These dosage forms facilitate intimate contact of the dosage form with the underlying absorption surface and allows modification of tissue permeability for absorption of macromolecules such as proteins and peptides. Incorporation of penetration enhancers like sodium taurocholate, sodium glycocholate and L-lysosphatidyl choline (LPC) and protease inhibitors in the mucoadhesive dosage forms results in the better absorption of peptides and proteins.

- Mucoadhesive drug delivery systems will prolong residence time of the dosage form on the application site and provide better absorption.
1.4.2. MECHANISM OF MUCOADHESION

Mucoadhesion is a complex process and many theories have been framed to explain the mechanisms involved. The mechanism of adhesion of certain macromolecules to the surface of a mucous tissue is not well understood yet. The mucoadhesive material must spread over the substrate to produce close contact and increase surface contact, to promote the diffusion of its chains within the mucus membrane. Attractive and repulsive forces arise and for a mucoadhesive property to be successful, the attractive forces must dominate\textsuperscript{30,31}.

However, many researchers have described the mucoadhesive bond formation as a three-step process.

- Spreading, wetting and swelling of the dosage form on the mucus surface, initiates intimate contact between the polymer and mucus layer. Mucoadhesives are able to adhere or bond with mucus by the help of the surface tension and forces that exist at the absorption or contact site. Swelling of polymers occurs because the components within the polymers have an affinity for water.

![Figure- 3: Mechanism of swelling](image)

- Inter-diffusion and inter-penetration take place between the chains of the mucoadhesive polymer and the mucus gel network, creating a greater area of contact. The mucoadhesive polymer chains and the mucosal polymer chains intermingle and entangle to form semi permeable adhesive bonds. The strength of these bonds depends upon the degree of penetration between the two polymer groups.
Entanglements and secondary chemical bonds are formed between the polymer chain and mucin molecules. The types of bonding formed between the chains include primary bonds such as covalent bonds and weaker secondary interactions such as Vander Waals interactions and hydrogen bonds\textsuperscript{32-34}.

**Figure-4: Mechanism of inter-diffusion and inter-penetration**

**Figure-5: Mechanism of entanglement**
1.4.3. MUCOADHESION THEORIES

Although the physical and chemical basis of mucoadhesion are not yet well understood, there are six theories developed from various studies based on the performance of several polymeric materials and polymer-polymer adhesion. They are

- Electronic Theory
- Adsorption Theory
- Wetting Theory
- Diffusion Theory
- Fracture Theory
- Mechanical Theory

**Electronic Theory**

Electronic theory is based upon the findings that both biological and mucoadhesive materials possess opposite electrical charges. Thus, when both the materials come into contact, they transfer electrons and establish a double electronic layer at the interface, where the attractive forces present within this electronic double layer decides the mucoadhesive strength.

**Adsorption Theory**

According to the adsorption theory, the mucoadhesive device adheres to the mucous by secondary chemical interactions, such as in hydrogen bonds and Vander Waals forces, hydrophobic interaction or electrostatic attractions. For example, hydrogen bonds are the common interfacial forces in polymers having carboxyl groups. Such forces have been considered as vital in the adhesive interaction phenomenon because, although they are individually delicate, a significant number of interactions can result in strong global adhesion.

**Wetting Theory**

The wetting theory applies to any liquid systems, which produce an affinity to a surface in order to spread over it. This affinity can be determined by measuring
techniques such as the contact angle. The general rule emphasis that lower the contact angle then the greater the affinity. The contact angle should be equal or close to zero to provide adequate spreadability.

**Diffusion Theory**

The diffusion theory states that the chains of mucoadhesive polymer and mucin interpenetrate to a sufficient depth (in the range of 0.2 to 0.5\(\mu\)m) to create a semi-permanent bond through entanglement. It is important that the components involved should have good solubility with each other, that is, both the bioadhesive and the mucus should have similar chemical structures. The greater the structural resemblance, the stronger the mucoadhesive bond.

**Fracture Theory**

According to this theory, the adhesive bond between systems is related to the force required to separate both surfaces form one another. This ‘fracture theory’ relates the force for polymer detachment from the mucus to the strength of their adhesive bond.

**Mechanical Theory**

This theory considers that adhesion arises from an interlocking of liquid adhesive into irregularities on the coarse surface. Rough surfaces provide an increased surface area available for interaction along with an enhanced viscoelastic and plastic dissipation of energy during joint failure, which are more important for the adhesion process than a mechanical effect\(^{35}\).
1.4.4. FACTORS AFFECTING MUCOADHESION

- **POLYMER RELATED FACTORS**
  
  **Molecular Weight**
  
  The optimum molecular weight for maximum mucoadhesion depends on the type of mucoadhesive polymers and tissue. Generally the threshold molecular weight required for successful mucoadhesion is at least 100,000 and beyond this level, there is little effect. The interpenetration of polymer molecules into the mucous layer is favorable for low molecular weight polymers whereas entanglements are important for high molecular weight polymers\[^{31}\].
  
  **Concentration of Polymer**
  
  There is an optimum concentration for a mucoadhesive polymer to produce maximum mucoadhesion. In a highly concentrated system, after the optimum point, the mucoadhesive strength drops appreciably because the coiled molecules get separated from the medium and polymeric chains available for interpenetration becomes very limited.
  
  **Flexibility of Polymer Chains**

  Chain flexibility of polymer is important for interpenetration and entanglement. As the water soluble polymers become cross-linked, the flexibility and mobility of the polymer chain decreases, thereby the effective length of the chain that penetrates through the mucus layer decreases, which in turn reduces the mucoadhesive strength.
  
  **Spatial Conformation**

  Mucoadhesive strength is based on the spatial conformation of polymers, i.e. linear or helical. The helical shape or structure of polymers may target many adhesively active groups responsible for adhesion, thereby reducing the adhesive strength of the polymer.
  
  **Swelling**

  Swelling characters are related to mucoadhesive itself and its environment. Swelling property is based on the polymer concentration, its ionic strength and the existence of water molecules.
ENVIRONMENT RELATED FACTORS

- **pH**
  The hydrogen ion concentration can control or influence the charge present in the surface of mucus as well as certain ionizable polymers. Mucus have a separate charge density that depends on pH, because of differences in dissociation of functional groups on amino acids and carbohydrate moiety of the polypeptide which may reduce adhesion.

- **Applied Strength**
  To locate a solid mucoadhesive system, it is vital to apply a defined strength. Whichever the polymer, the adhesive strength of those polymers increase with the increase in the applied strength.

- **Initial Contact Time**
  The initial contact time between mucus layer and mucoadhesive polymer determines the degree of swelling and the interpenetration of polymer chains. The adhesive strength increases as the initial contact time between mucus layer and mucoadhesive polymer increases.

PHYSIOLOGICAL FACTORS

- **Mucin Turnover**
  Mucoadhesive polymers are detached from the mucus surface due to mucin turnover irrespective of their mucoadhesive strength.

- **Disease state**
  The physicochemical properties of the mucus may alter during disease conditions such as gastric ulcers, common cold, cystic fibrosis, ulcerative colitis, fungal and bacterial infections and inflammatory conditions within the eye. If mucoadhesive dosage forms are to be used in the disease conditions, the mucoadhesive property is required to be evaluated under the similar conditions\textsuperscript{36,37}.  

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1.5. MUCOADHESIVE DOSAGE FORMS

The primary objectives of mucoadhesive dosage forms are to provide intimate contact of the dosage form with the absorbing surface and to increase the residence time of the dosage form at the absorbing surface to prolong drug action\textsuperscript{38,39}. The mucosal layer lies in a number of regions of the body including the respiratory airways, the nose, ear, eye, gastrointestinal tract and urogenital tract. These mucosal areas represent potential sites for adherence of any mucoadhesive systems and hence; the mucoadhesive drug delivery system may include the following:

- Nasal delivery systems
- Ocular delivery systems
- Buccal delivery systems
- Vaginal delivery systems
- Rectal delivery systems
- Gastrointestinal delivery systems

\textbf{Nasal Drug Delivery System}

Use of mucoadhesive drug delivery system will increase the residence time of formulations in the nasal cavity, thereby improving the absorption of drugs. The use of dry powder formulations containing mucoadhesive polymers for nasal administration of peptides and proteins was first investigated by Nagai \textit{et al.} Beconase nasal spray is used to treat nasal inflammation and nasal allergies associated with hay fever. The spray contains the drug Beclomethasone dipropionate and the mucoadhesive polymer carboxy methyl cellulose and microcrystalline cellulose. Morimoto \textit{et. al.} developed mucoadhesive system for nasal administration of Nifedipine.

\textbf{Ocular Drug Delivery System}

There are several mucoadhesive dosage forms that have been developed for ocular drug delivery: liquid system, \textit{in situ} gelling system, dispersed system and solid system. Various mucoadhesive systems employed for ocular delivery of drugs include the semi-
solids, viscous liquids, solids/inserts and the particulate drug delivery systems, including mucoadhesive microspheres and liposomes. Gel tears and Viscoatears Liquid gel eye drops are used for dry eye conditions and contain carbomer 980 (polyacrylic acid). Carbomer lubricate the eye by clinging onto the surface of the eye thereby reducing the frequency of application to the eye. The advantages of microspheres, i.e., increased residence time and decreased frequency of administration, were quite evident with chitosan microspheres of Acyclovir and Methyl Prednisolone loaded Hyaluronic acid microspheres.

**Buccal Drug Delivery System**

Because of the presence of a smooth and relatively immobile surface the region of the buccal cavity appears to be more suitable for controlled or sustained delivery of therapeutic agents using mucoadhesive drug delivery system. Drugs with a short biological half-life requiring a controlled or sustained release effect and having poor permeability or poor solubility, susceptibility to enzymatic degradation are good candidates to be delivered via the oral cavity. Robinson *et al.* showed that a three-layer buccal patch, containing a rate-limiting middle membrane, an impermeable backing membrane and a basement membrane containing poly carbophil, can remain in place for up to 15 h in humans, regardless of eating or drinking. Suscard is a buccal tablet containing Glyceryl trinitrate drug used for the treatment of angina. It contains the mucoadhesive agent Hydroxypropyl methyl cellulose.

**Vaginal Drug Delivery System**

Vaginal route has been used for the delivery of drugs, which are susceptible to gastrointestinal degradation or hepatic metabolism following peroral delivery e.g. Oestrogens and Progestogens in the treatment of postmenopausal symptoms and for contraception. This route has also been explored for the delivery of therapeutic peptides, such as Calcitonin and for microbicidal agents to help prevent the transmission of human immuno-deficiency virus and other sexually transmitted diseases. Recently, vaginal mucoadhesive preparations have been developed as a new type of controlled release form for the treatment of both topical and systemic diseases. Robinson *et. al.* reported on a system of treatment using a gel containing the mucoadhesive polycarbophil that remained on vaginal tissue for 3-4 days and hence served as a platform for delivery of drug such as
Progesterone. Mucoadhesive polymers are incorporated into vaginal formulations to aid the adhering of dosage forms to its target site. Polymers may also prolong the retention of the drug in the vaginal cavity and also optimize the reach of mucoadhesive formulation over the vaginal epithelial cells.

- **Rectal Drug Delivery System**

  Another way to deliver the drug by using mucoadhesive polymers is through the mucous membrane of the rectum. It is an important route of administration for drugs that have severe gastrointestinal side effects. Rectal route is also suitable for unconscious patients, infants and patients who cannot take medicines through oral route. The drugs absorbed from the rectal mucosa can escape from the breakdown by hepatic enzymes. Because of this reason mucoadhesive suppositories have been developed for the local treatment of diseases in rectal cavity such as hemorrhoids and rectal cancer. Hydrogels administered rectally have proven to be useful for drug delivery. Leede *et. al.* proposed hydrogels using hydroxy ethyl methacrylate cross-linked with ethylene glycol dimethacrylate and including Antipyrine and Theophylline as model drugs provided rate-controlled drug delivery. Anacal is a rectal ointment used to relieve the symptoms associated with hemorrhoids. It contains the mucoadhesive agent polyethylene high polymer 1500.

- **Gastro-intestinal Mucoadhesive Drug Delivery System**

  The idea of mucoadhesive began with the clear need to localize a drug at certain sites in the GIT. Therefore, a primary objective of using mucoadhesive systems orally would be achieved by obtaining a substantial increase in residence time of the drug for local or systemic effect and to permit once a daily dosing. A number of mucoadhesive dosage forms, including sustained release tablets, powders, semi-solid forms, nanoparticles and microparticles have been widely studied in the GIT. Mucoadhesive drug delivery systems form an important approach to decrease the GI transit of drugs. The GI epithelium consists of a single layer of simple, columnar epithelium lying above a collection of cells called the lamina propria and supported by a layer of smooth muscle know as the muscularis mucosae. Tight junctions or the zona occludens hold the cells together. A special type of GI epithelium, the Peyer’s patches (PP) of the gut associated
lymphoid tissue (GALT), is present. Polymeric microspheres can also be phagocytized by this microfold cells and hence can be used for vaccination purposes. Specially engineered polymeric mucoadhesive microspheres can traverse both the mucosal absorptive epithelium and follicle-associated epithelium covering the lymphoid tissues of the Peyer’s patches, depending upon the particle size, polymer composition and the surface charge of mucoadhesive microspheres.

Colon drug delivery has been used for molecules aimed at local treatment of colonic diseases and for delivery of molecules susceptible to enzymatic degradation, such as peptides. The mucosal surface of the colon resembles that of the small intestine at birth but changes with age, causing the loss of villi leaving a flat mucosa with deep crypt cells. Therefore, the absorptive capacity of the colon is much less compared to the small intestine. Mucoadhesive microspheres can be used during the early stages of colonic cancer for enhancing the absorption of peptide drugs and vaccines, for the localized action of steroids and drugs with a high hepatic clearance (e.g. Budesonide) and for the immunosuppressive agents such as Cyclosporine. Colonic-specific mucoadhesive microspheres can be used for protection of peptide drugs from the enzyme rich part of the GIT and to release the biologically active drug at the desired site for its maximum absorption.
1.5.1. MUCOADHESIVE MICROENCAPSULATION

Microspheres form an important part of novel drug delivery systems. The success of microspheres is limited due to their short residence time at the absorption site. Therefore it is advantageous to have a method for providing an intimate contact of the mucoadhesive drug delivery systems with the absorbing membrane. The intimate contact can be established by combining the mucoadhesion characteristics to microparticles and developing mucoadhesive microparticles. Mucoadhesive microparticles have advantages like efficient absorption and improved bioavailability of drugs due to high surface-volume ratio, a much more intimate contact of drug with the mucosal layer and specific targeting of drugs at the site of absorption. Mucoadhesive microparticles that retained on the GIT would increase the absorption, decrease dosing frequency and provides better patient compliance when compared to conventional dosage forms. Gastric mucoadhesive drug delivery offers a number of applications for drugs having poor bioavailability because of narrow absorption window in the upper part of gastrointestinal tract.

The concept is based on the self-protecting mechanism of the GIT. Mucus secreted continuously by the specialized goblet cells located throughout the GIT plays a cytoprotective role. The epithelial adhesive properties of mucin are well known and have been applied to the development of mucoadhesive drug delivery systems through the use of mucoadhesive polymers. Retention of a mucoadhesive drug delivery system in the specific region of the gastrointestinal tract increases the intimacy and duration of contact between a drug containing mucoadhesive polymer and mucous surface, thereby prolonging the action of the drug.
Figure- 6: Interaction of mucoadhesive drug delivery system and mucin of the gastro intestinal tract

Figure- 7: Retention of mucoadhesive drug delivery systems in the stomach
1.5.2. MUCOADHESIVE POLYMERS

Mucoadhesive polymers are synthetic or natural macromolecules, which are capable of attaching to mucosal surfaces. The concept of mucoadhesive polymer has been introduced into the pharmaceutical literature, more than 40 years ago and now-a-days it has been accepted as a promising strategy to prolong the residence time and to improve the specific localization of drug delivery system on various membranes\(^4\). Mucoadhesive formulations utilize the polymers as adhesive component. These formulations are usually water soluble and as in a dry form can attract water molecules from the biological surface and this may leads to an exciting 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 that stick or adhere to the mucin-epithelial surface can be divided into three broad ranging classes.

- Polymers that become adhesive when put in water and owe their mucoadhesion to stickiness.
- Polymers that stick or adhere through non-specific, non-covalent type interactions those are basically electrostatic in nature.
- Polymers that bind to a specific receptor site on tile self surface.

1.5.3. Characteristics of an Ideal Mucoadhesive Polymer

- Polymers and their degradation components should be non-irritant, non-toxic and free from impurities\(^3\).
- It should have good wetting, spreadability, solubility, swelling, and biodegradability properties.
- It should not be affected by the food intake, hydrodynamic conditions and change of pH.
- It should adhere quickly to the mucosa.
- It should possess peel, shear and tensile strengths at the mucoadhesive range.
- Polymers must be easily available and its cost should not be high.
- It should exhibit mucoadhesive properties in the both dry and liquid state.
- It should reveal penetration enhancement characteristics.
• It should possess acceptable shelf-life period.
• It should possess optimum molecular weight.
• It should possess required and essential spatial conformation.
• It should have adequate cross-linking characteristics but not upto the level of suppression of bond establishing groups.
• It should not assist in development of secondary infections, e.g. Dental caries, which is mainly noticed in mucoadhesive buccal drug delivery systems.

1.5.4. Classification of Mucoadhesive Polymers

| Semi-Natural/Natural | Chitosan, agarose, Hyaluronic acid, gelatin, various gums (guar, xanthan, carrageenan, gellan, pectin and sodium alginate), starch, sulfated polysaccharides. |
| Synthetic Cellulose Derivatives | Carboxy methyl cellulose (CMC), CMC sodium, Hydroxy ethyl cellulose (HEC), Hydroxypropyl cellulose (HPC), Hydroxypropyl methyl cellulose (HPMC), Methyl cellulose (MC), methyl hydroxy ethyl cellulose. |
| Synthetic Poly (acrylic acid) Based Polymers | Polycarbophil, carbopel, polyacrylates, poly (methyl vinyl ether-co-methacrylic acid), poly (2-hydroxyethyl methacrylate), poly (acrylic acid-co ethyl hexyl acrylate), poly (methacrylate), poly (alkyl cyano acrylate), poly (isohexylcyanoacrylate), poly (isobutylcyanoacrylate), copolymer of acrylic acid and Poly ethylene glycol. |
| Miscellaneous | Poloxamers, polyoxy ethylene, poly vinyl alcohol, polyvinyl pyrolidone and thiolated polymers. |
1.6. FORMULATION OF MUCOADHESIVE MICROSPHERES AND MICROCAPSULES

Mucoadhesive microspheres and microcapsules can be prepared by using any of the following methods:

- Hydrogel Microspheres
- Single Emulsion Method
- Double Emulsion Method
- Polymerization Method
- Phase Separation Coacervation Method
- Spray Drying and Spray Congealing Method
- Solvent Removal Method
- Solvent Evaporation Method
- Solvent Extraction Method
- Phase Inversion microencapsulation
- Hot Melt Microencapsulation

- Hydrogel Microspheres

Hydrogel microspheres are made up of gel-type polymers. They are produced by dissolving the polymer in aqueous solution, dispersing the active medicament in the mixture and forcing the resultant dispersion through a precision device to produce micro-droplets of the mixture, which may then fall into a congealing bath containing calcium chloride solution that will crosslink the polymer during gentle stirring to form gelled microspheres. This method involves aqueous system and no residual solvents. The size of microspheres formed can be controlled by using several size extruders or by varying the flow rate polymer solution.

- Single Emulsion Method

The micro-particulate carriers of natural polymers, i.e. those of carbohydrates and proteins are prepared by single emulsion method. The natural polymers are first dissolved or dispersed in aqueous medium followed by dispersion in the non-aqueous medium such as oil followed by cross linking of the dispersed globule. This can be achieved either by normal heat process or by chemical cross linking agents. The chemical cross linking
agents used are formaldehyde, glutaraldehyde etc. Finally the microparticles formed were washed, collected and air dried.

- **Double Emulsion Method**

  Double emulsion method used for the preparation of microparticles may involve the formation of the multiple emulsions and is best suited for water soluble drugs, proteins, vaccines and peptides. Both the natural as well as synthetic polymers can be used in this method. The aqueous solution of protein containing the drug or active constituent is dispersed in a lipophilic organic continuous phase. The continuous phase usually consists of polymer solution that finally encapsulates the protein present in the dispersed aqueous phase. The primary emulsion formed is subjected to sonication or homogenization before adding to the aqueous solution of the poly vinyl alcohol (PVA). This results in the formation of a double emulsion which is then subjected for solvent removal either by solvent extraction or solvent evaporation method.

- **Polymerization Method**

  The polymerization methods used for the production of the microparticles are

- **a. Normal Polymerization**

  It is carried out using different techniques such as bulk, suspension, emulsion and micellar polymerization processes. In bulk polymerization method a monomer or mixture of monomers along with the catalyst were heated to initiate polymerization. The loading of drug may be done during the polymerization process. Suspension polymerization is carried out by heating monomer or mixture of monomers as droplet dispersion in a continuous phase. The dispersion may contain initiator and other additives. In emulsion polymerization the initiator will be present in the aqueous phase, which later-on diffuses towards the surface of micelles.

- **b. Interfacial Polymerization**

  In interfacial polymerization method, reaction of several monomers occurs at the interface between the two immiscible liquid phase to form a polymer film that coats the dispersed phase.
Phase Separation Coacervation Method

This method is based on the principle of reducing the polymer solubility in organic phase to effect the coacervates formation. In this process, the drug particles are dispersed in a polymer solution and to this an incompatible polymer is added which makes the first polymer to phase separate and coat the drug particles. Addition of a non-solvent results in the solidification of polymer. The process variables are very important since the rate of achieving the coacervates determine the distribution of the particle size, polymer film and agglomeration of the formed particles. The agglomeration may be avoided by stirring the suspension, since as the process of microspheres formation starts, the polymerized globules will start to stick and form agglomerates.

Spray Congealing and Spray Drying Method

This method is based on the drying mist of the polymer and drug in the air. Depending on the cooling of the polymeric solution or removal of the solvent system, the two processes are named as spray congealing and spray drying respectively. In this process, the polymer is dissolved completely in an organic solvent such as acetone or dichloromethane etc. The core material is then dispersed into the polymer solution using a high speed homogenizer. This dispersion is then atomized into a thin stream of hot air that leads to the formation of the fine mist or the small droplets from which the solvent evaporates rapidly leading to the formation of microparticles. Finally the microparticles are separated using cyclone separator while the solvents are removed by vacuum drying.

Solvent Removal method

It is a non-aqueous method particularly suitable for water labile polymers. In this method, drug is dissolved or dispersed in a polymer using a volatile organic solvent like methylene chloride. This mixture is then added in silicone oil containing mixture of span 80 and methylene chloride. After pouring the polymer solution, petroleum ether is added and stirred continuously until the solvent is extracted into the oil solution.

Solvent Evaporation Method

In this method, a plain aqueous solution of the drug is added to an organic phase like ethyl acetate or dichloromethane or chloroform in which polymer is dissolved. The solution is stirred vigorously to form the primary w/o emulsion. This is then added to a large volume of aqueous solution containing an emulsifier like PVP or PVA to form a
multiple emulsion. The multiple emulsion is finally stirred to evaporate the organic solvent to produce microspheres. The microspheres are then washed, centrifuged and freeze dried.

- **Solvent Extraction Method**

  This method involves removal of the organic phase by extraction of the organic solvent. The method involves the use of water-miscible organic solvent such as Isopropanol. In this, the organic phase is removed by extraction with water. This will decrease the hardening time of microparticles. The rate of solvent removal by extraction method depends upon the ratio of emulsion volume, temperature of water and the solubility profile of the polymer.

- **Phase Inversion Microencapsulation**

  This process involves the addition of drug to a dilute solution of the polymer (usually 1-5%, w/v in methylene chloride). The mixture is poured into an unstirred bath of non-solvent (petroleum ether) in a ratio of 1:100, resulting in the spontaneous production of microspheres. The resulting microspheres are filtered, washed and dried. This method is simple, rapid and involves relatively little loss of drug and polymer.

- **Hot Melt Microencapsulation**

  In this method, the polymer is melted and mixed with solid particles of the drug. The mixture is suspended in a non-miscible solvent (silicone oil), continuously stirred and heated to 5°C above the melting point of the polymer. Finally the emulsion is allowed to stabilize and cooled until the particles solidify. The resulting microspheres are washed with petroleum ether. The primary objective of this method is to develop a microencapsulation process suitable for the water labile polymers e.g. Polyanhydrides. Microspheres with a diameter of 1-1000 µm can be obtained by this method.\(^{43,44}\).