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AN OVERVIEW: SITE SPECIFIC DRUG DELIVERY SYSTEM

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Abstract

The drug delivery system is to provide a therapeutic amount of drug to a proper site in body so that the desired concentration can achieved promptly and then maintained. Site specific drug delivery refers to targeting a drug directly to a certain biological location. Targeted drug delivery implies selective and effective localization of drug into the target at therapeutic concentrations with limited access to non target sites. Recently, greater emphasis has been placed on controlling the rate and or site of drug release from oral formulations for the purposes of improving patient compliance and treatment efficacy. Benefits of site specific drug delivery Drug directly available at the target site, Decrease in dose to be administered, Decrease side effect, improve drug utilization; it is a promising site for drugs which are unstable or poorly absorbed at upper GI tract. It is a challenging task to formulate such kind of drug delivery system.

Keywords: *targeted drug delivery, site specific drug delivery, Pharmacokinetic, Pharmacodynamic, sustained drug delivery.*

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INTRODUCTION

Oral drug delivery system is the preferred route being user friendly route of administration, as non-invasive mode of delivery and has good level of patient compliance and flexibility in formulation. Conventional oral dosage forms provide a specific drug concentration in systemic circulation without offering any control over drug delivery. These systems achieve, as well as, maintain drug concentration within therapeutically effective range needed for treatment only when taken several times a day, resulting in significant fluctuation of drug levels in the systemic circulation. For various chronic diseases generally oral therapy is given as required for long term [1].

Site Specific Drug Delivery Systems

The goal of any drug delivery system is to provide a therapeutic amount of drug to a proper site in body so that the desired drug concentration can achieved promptly and then maintained. That is drug delivery system should deliver drug at a rate dictated by the needs of the body over a specified period of time. Site specific drug delivery refers to targeting a drug directly to a certain biological location.

Targeted drug delivery implies selective and effective localization of drug into the target at therapeutic concentrations with limited access to non target sites. A targeted drug delivery system is preferred in the following situation;

- **Pharmaceutical** : Drug instability, low solubility
- **Pharmacokinetic** : Short half life, poor absorption
- **Pharmacodynamic** : Low specificity, low therapeutic index

The shift from conventional sustained release approach to modern pulsatile delivery of drugs can be credited to the following reason(s):

- **Gastric Irritation**

Some drugs show negative effect on gastric mucosa, need to be deliver into the intestine region in order to reduce its side effects. e.g. Sodium Diclofenac is a widely used nonsteroidal anti-inflammatory drug (NSAID) that exhibits anti rheumatic, analgesic, osteoarthritis, and antipyretic activities. The most common adverse effects of the drug are gastritis, peptic ulceration Because of the short biological half-life and associated adverse effects, it is planned to prepare a chitosan/carrageenan gel beads as a new controlled drug release system for Diclofenac to offers site specific delivery of drug in intestine thereby enhancing bioavailability and reduction of dose size [2].

- **Drug Instability In Gastric Fluid**

Generally, proteins and peptides as well as proton pump inhibitors are sensitive o the hostile environment of stomach; hence it is necessary to formulate a suitable drug delivery system in order to counteract acid degradation effect.

e.g. A pH-sensitive and mucoadhesive thiolated eudragit-coated chitosan microsphere of Pentaprazole is formulated in order to prevent its acid degradation in hostile environment of stomach [3].

- **Drug Absorption Differences In Various Gastrointestinal Segments**

In general, drug absorption is moderately slow in the stomach, rapid in the small intestine, and sharply declining in the large intestine. Compensation for changing absorption characteristics in the gastrointestinal tract may be important for some drugs.

e.g. Buparvaquone being poorly water soluble drug shows poor absorption from stomach environment, hence it is need to be deliver to the intestine region with enhanced bioavailability [4].

- **Local Therapeutic Need**

For the treatment of local disorders such as inflammatory bowel disease, the delivery of compounds to the site of inflammation with no loss due to absorption in the intestine region is highly desirable to achieve the therapeutic effect and to minimize side effects.

e.g. In order to get localized effect ,a multiparticulate delivery system for site-specific delivery of 5-fluorouracil (FU) using natural polysaccharides (pectin) and pH-sensitive polymer (Eudragit S100) for the treatment of colon cancer was designed successfully [5].

- **Stability of Method**

The chitosan based multiparticulate system is generally prepared with the help of various methods like, tripolyphosphate cross linking (TPP) and emulsification ionotropic gelation with NaOH (EIG) as well as glutaraldehyde chemical cross linking method (GCL). But their acidic disruption, results in faster drug liberation in acid environment of stomach. To suppress this initial burst release, it is necessary to coat these microparticles with pH- dependent polymer to deliver intact drug molecule into distal part of intestine [6].

e.g. The chitosan-GCL microparticles of 5-fluorouracil (FU) shows faster drug release in gastric fluid. So, enteric coating to these microparticles is the one of the approach to protect drug loss in upper part of GIT [7].

Site specific drug delivery system is also called as "*SMART SYSTEM*" consists of a triggering mechanism, responding only to the true physiological conditions particularly to small intestine. It is a site where both local and systemic drug delivery can take place. Treatment might be more effective if the drug substances were targeted directly on the site of action

in the intestine. Lower doses might be adequate and, if so, systemic side effects might be reduced.

Recently, greater emphasis has been placed on controlling the rate and or site of drug release from oral formulations for the purposes of improving patient compliance and treatment efficacy. A reduced dosing frequency and improved patient compliance can also be expected for the sustained release drug delivery systems, compared to immediate release preparations [8]. The small intestine is a region of the gastrointestinal tract that would benefit from the development and use of such modified release technologies [9].

A therapeutic Advantage of Targeting Drug to the Specific Region Includes

- The ability to cut down the conventional dose
- Reduced the incidence of adverse side effects
- Delivery of drug in its intact form as close as possible to the target sites.

Site specific drug delivery systems are also gaining importance for the delivery of

protein and peptides due to several reasons as follow:

- ✓ Larger surface area for absorption
- ✓ Longer residence time
- ✓ Responsiveness to absorption enhancers
- ✓ Trans mucosal and membrane potential difference drops is significant in the

absorption of the ionized and unionized drugs

- ✓ Wall of small intestine has a network of both blood and lymph vessels [10, 11].

oral delivery is considered better than other dosage form like rectal delivery (suppositories and enemas) due to their lack of efficacy and a high variability in distribution of drugs, e.g. suppositories are effective only in rectum due to their confined use and while enemas solution can offer only topical treatment to the sigmoid and descending colon. Thus, oral route is preferred but the absorption and dissolution in upper part of gastrointestinal tract is the major obstacle and must be circumvented for successful site delivery.

Benefits of Site Specific Drug Delivery

1. Drug directly available at the target site
2. Decrease in dose to be administered
3. Decrease side effect
4. Improve drug utilization
5. It is a promising site for drugs which are unstable or poorly absorbed at upper GI tract.

Problems Associated With Site Specific Drug Delivery System

1. It is a challenging task to formulate such kind of drug delivery system.
2. It is possible that enteric coating alone may not be

for the premature drug release in the stomach depending upon the GI motility patterns which can widely vary in individual patients and in different disease states.

3. The failure of the coating to dissolve may also occur particularly when the pH of small intestine that is below normal in patients with meal [12].To certain extent, the longer residence time may compensate for these limitations.

Anatomy and Physiology of Small Intestine

Gross Anatomy

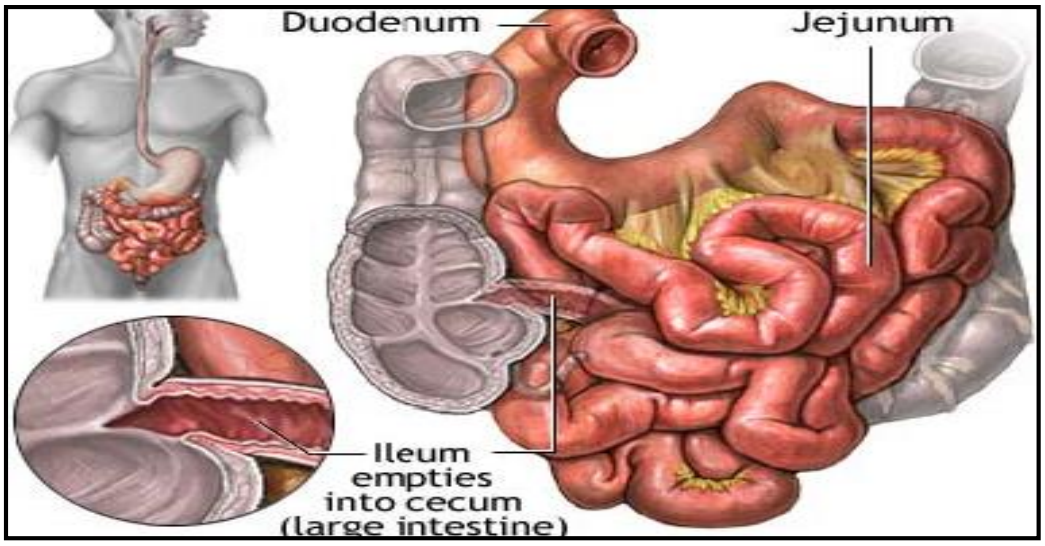

Fig 1: Basic Anatomy of The Digestive System [13]

The gastrointestinal tract is divided into stomach, small intestine and large intestine. The small intestine is the longest section of the digestive tube and consists of three segments forming a passage from the pylorus to the large intestine.

- **Duodenum:** A short section that receives secretions from the pancrease and liver via the pancreatic and common bile ducts.
- **Jejunum :** Considered to be roughly 40% of the small gut in man, but closer to 90% in animals.
- **Ileum :** Empties into the large intestine; considered to be about 60% of the intestine in man, but veterinary anatomists usually refer to it as being only the short terminal section of the small intestine.

Its main functions are:

- **Digestion:** The process of enzymatic digestion, which began in the stomach, is completed in the small intestine.
- **Absorption:** The small intestine is the region where more nutrients and other materials are absorbed. The wall of the small intestine has a rich network of both blood and lymphatic vessels. The gastrointestinal circulation is the largest systemic regional vasculature and nearly a third of cardiac output flows through the gastrointestinal vice versa [14].

Microscopic Anatomy

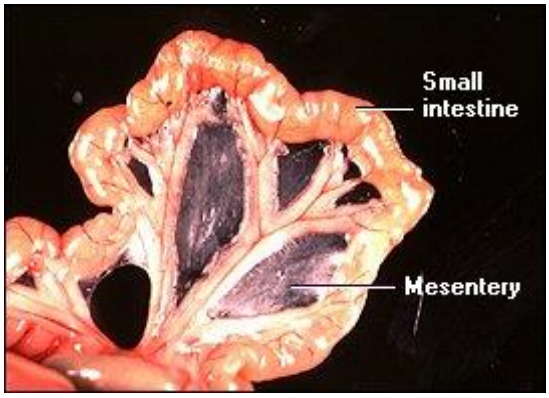

Fig 2: Microscopic cross section of small intestine

A bulk of the small intestine is suspended from the body wall by an extension of the peritoneum called the mesentery. As seen in the image, blood vessels to and from the intestine lie between the two sheets of the mesentery. Lymphatic vessels are also present, but are not easy to discern grossly in normal specimens. The lymphatic system is important in the absorption of fats from the gastrointestinal tract.

In the ileum, areas of lymphoid tissue close to the epithelial surface which are known as peyer's patches. These cells play a key role in the immune response as they transport macromolecules and are involved in antigen uptake [15,16].

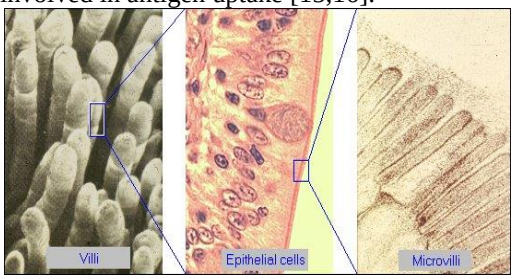

Fig3: Structure of Villus

If the small intestine is viewed as a simple pipe, its luminal surface area would be on the order of one half of a square meter. But in reality, the absorptive surface area of the small intestine is roughly 250 square meters.

The small intestine incorporates three features which account for its huge absorptive surface area:

- **Mucosal folds:** the inner surface of the small intestine is not flat, but thrown into circular folds, which not only increase surface area, but aid in mixing the ingest by acting as baffles.
- **Villi:** the mucosa forms multitudes of projections which protrude into the lumen and are covered with epithelial cells.
- **Microvilli:** the luminal plasma membrane of absorptive epithelial cells is studded with densely-packed microvilli.

The panels shown in above **Figure No.3**, depicts the bulk of this surface area expansion, showing villi, epithelial cells that cover the villi and the microvilli of the epithelial cells. Note in the middle panel, a light micrograph, that the microvilli are visible and look something like a brush. For this reason, the microvillus border of intestinal epithelial cells is referred to as the "**brush border**" [17].

Approaches to Deliver Intact Drug Molecule to Small Intestine

Successful site specific delivery requires careful considerations of number of factors including the properties of drug, the type of delivery and its interaction with the healthy or diseased gut.

The other commonly used approaches are:

1. pH dependent delivery,
2. Time dependent delivery,
3. Pressure dependent delivery,
4. Embedding in matrices.

(Combination of any of the above approaches can also be use)

pH Dependent Drug Delivery

The pH-dependent systems exploit the generally accepted view that pH of the human GIT increases progressively from the stomach (pH 1-2 which increases to 4 during digestion), small intestine (pH 6-7) at the site of digestion and it increases to 7-8 in

the distal ileum. The coating of pH-sensitive polymers to the tablets, capsules or pellets provide delayed release and protect the active drug from gastric fluid. The polymers used for enteric coating , however, should be able to withstand the lower pH values of the stomach and of the proximal part of the small intestine and also be able to disintegrate at the neutral or slightly alkaline pH of the terminal ileum. These processes distribute the drug throughout the intestine and improve the potential of targeted delivery systems. While this release pattern can be studied *in vitro*, there is no real substitute for confirming reliable performance *in vivo* in man. The technique of γ- scintiography has become the most popular method to investigate the gastrointestinal performance of pharmaceutical dosage forms. The most commonly used polymer for this purpose is methacrylic acid and methyl methacrylate that dissolve at pH 6 (Eudragit L) and pH 7 (Eudragit S, FS) have been investigated. This approach is based on the fact that the gastrointestinal pH is increase progressively from small intestine to colon.

Time Dependent Drug Delivery

This approach is based on the principle of delaying the release of the drug until it enters into its site of absorption. Although gastric emptying tends to be highly variable, small intestinal transit time is relatively constant or little bit variation can be observed. The strategy in designing timed-released systems is to resist the acidic environment of the stomach and to undergo a lag time of predetermined span of time, after which release of drug take place. As a new oral enteric coated timed-release press-coated tablet (ETP tablets) were developed by coating enteric polymer on timed-release press-coated tablets composed of an outer shell of hydroxypropylcellulose and core tablet containing Diltiazem hydrochloride as a model drug.

Pressure Dependent Delivery

The OROS-CT (Alza Corporation) can be used to target the drug locally to the colon for the treatment of disease or to achieve systemic absorption that is otherwise unattainable.

The OROS-CT system can be single osmotic unit or may incorporate as many as 5-6 push-pull units, each 4mm in diameter, encapsulated within a hard gelatin capsule. Each bilayer push pull unit contains an osmotic push layer and a drug layer, both surrounded by a semipermeable membrane. An orifice is drilled through the membrane next to the drug layer. Immediately after the OROS-CT is swallowed, the gelatin capsule containing the push-pull units dissolves. Because of its drug-impermeable enteric coating, each push-pull unit is prevented from absorbing water in the acidic aqueous environment of the stomach and hence no drug is delivered**.** As the unit enter the small intestine, the coating dissolve in this higher pH environment (pH >6), water enters the unit, causing the osmotic push compartment to swell and concomitantly creates a flowable gel in the drug compartment. Swelling of the osmotic push compartment forces drug gel out of the orifice at a rate precisely controlled by the rate of water transport through the semipermeable membrane.

Embedding in Matrices

The drug molecules are embedded in the polymer matrix. The polymers used for this technique should exhibit degradability in the small intestine results into the liberation of entrapped drug. A novel oral sustained delivery of Aceclofenac is designed with the help of sodium alginate have an acid resident property showing fastest drug release when reaches to the small intestine [18,19].

Table 1: Examples of the some Site Specific Formulations with Different Strategies

Technique	Polymer (s) used	Drug	Ref.
pH dependent	Eudragit S & L100	Indomethacin	**20**
	Thiolated Eudragit L100	BSA	**21**
Time dependent	Eudragit L100	Piroxicam	**22**
Embedding in matrices	**Sodium alginate**	**Aceclofenac**	**19**

Table 2: Examples of Site Specific Marketed Formulations

Drug	Trade Name	Formulation	Dose
Mesalamine	Salofac	Eudragit-L coated tablets	**1.0-4.0 gm/day**
Mesalamine	Claversal	Eudragit-L coated tablets	**1.0-2.0 gm/day**
Budesonide	Entocort	Eudragit-L coated beads	**9 mg/day**
Sulphasalazine	**Colo-pleon**	**Eudragit L 100-55**	**-**

Bioadhesive Drug Delivery System

Interest in controlled and sustained release drug delivery has increased considerably during the past decade and, in selected areas, it is now possible to employ fairly sophisticated systems which are capable of excellent drug release control. The self regulating insulin delivery systems by using lectins and oral osmotic tablet are illustrative examples. However, for oral administration, all of these systems are limited to some extent because of gastrointestinal (GI) transit. Thus, the duration of most oral sustained release products is approximately 8-12 hours due to relatively short GI transit time, and the possibilities to localize a drug delivery system in selected regions of the gastrointestinal tract for the purpose of localized drug delivery are under investigation. Several approaches have been suggested to increase GI transit time, addressing the issue of localized drug delivery. A possible approach is to employ bioadhesive polymers that adhere to the mucin / epithelial surface [23].

Bioadhesion / Mucoadhesion

The polymeric system would be immobilized at the gastrointestinal surface by an adhesion mechanism, which is referred to as "bioadhesion". However, when these adhesive interactions are restricted to the mucus layer lining the mucosal surface, the term "mucoadhesion" is also employed. All of these adhesive phenomena may result in either: (i) an increase of the residence time of the pharmaceutical dosage form in close contact with the mucosa, or (ii) a localization of the delivery system in a particular region of the gut.

Bioadhesive polymeric systems have been used since long time in the development of products for various biomedical applications which include denture adhesives and surgical glue. The adhesion of bacteria to the human gut may be attributed to the interaction of lectin-like structure (present on the cell surface of bacteria) and mucin (present in the biological tissues) .In general, various biopolymers show the bioadhesive properties and have been utilized for various therapeutic purposes in medicine. The bioadhesive polymers can be broadly classified into two groups, namely specific and nonspecific. The specific bioadhesive polymers (e.g. lectins, fimbrin) have the ability to adhere to specific chemical structures within the biological molecules while the nonspecific bioadhesive polymers (e.g. polyacrylic acid, cyanoacrylates) have the ability to bind with both the cell surfaces and the mucosal layer.

Mechanism of Mucoadhesion

A complete understanding of how and why certain macromolecules attach to a mucus surface is not yet available, but a few steps involved in the process are generally accepted, at least for solid systems:

- ✓ Spreading, wetting and swelling of the dosage form at the mucus surface, initiates intimate contact between the polymer and mucus layer.
- ✓ Interdiffusion and interpenetration takes place between the chains of the mucoadhesive polymer and the mucus gel network, creating a greater area of contact.
- ✓ Entanglements and secondary chemical bonds are formed between the polymer chain and mucin molecules [24,25].

It has been stated that at least one of the following polymer characteristics are required to obtain adhesion : (a) sufficient number of hydrogen bonding chemical groups (-OH and –COOH) (b) anionic surface chain (c) high molecular weight (d) high chain flexibility (e) surface tension that will induce spreading into the mucus layer. Each of these characteristics favours the formation of bonds that are either chemical or mechanical origin.

Theories of Mucoadhesion

The phenomenon of bioadhesion occurs by a complex mechanism. Till date, six theories have been proposed which can improve our understanding for the phenomena of adhesion and can also be extended

to explain the mechanism of bioadhesion. The theories include: (a) the electronic theory, (b) the wetting theory, (c) the adsorption theory, (d) the diffusion theory, (e) the mechanical theory and (f) the cohesive theory.

A. Electronic theory

The electronic theory proposes transfer of electrons amongst the surfaces resulting in the formation of an electrical double layer thereby giving rise to attractive forces.

B. Wetting Theory

The wetting theory postulates that if the contact angle of liquids on the substrate surface is lower, then there is a greater affinity for the liquid to the substrate surface. If two such substrate surfaces are brought in contact with each other in the presence of the liquid, the liquid may act as an adhesive amongst the substrate surfaces.

C. Adsorption Theory

Adsorption theory proposes the presence of intermolecular forces, viz. hydrogen bonding and Van der Waal's forces, for the adhesive interaction amongst the substrate surfaces.

D. Diffusion Theory

The diffusion theory assumes the diffusion of the polymer chains, present on the substrate surfaces, across the adhesive interface thereby forming a networked structure.

E. Mechanical Theory

It explains the diffusion of the liquid adhesives into the micro-cracks and irregularities present on the substrate surface thereby forming an interlocked structure which gives rise to adhesion.

F. Cohesive Theory

The cohesive theory proposes that the phenomena of bioadhesion are mainly due to the intermolecular interactions amongst like-molecules. Based on the above theories, the process of bioadhesion can be broadly classified into two categories, namely chemical (electronic and adsorption theories) and physical (wetting, diffusion and cohesive theory) [26]

Factors Affecting Mucoadhesion

Based on the theories of the adhesion, it can be summarized that the mucoadhesive property of a polymer can be tailored by changing the parameters which has the capacity to alter the interaction among the polymer and the mucosal layer. In this section, attempts will be made to analyze some of the parameters which can tailor the mucoadhesive property of a given polymer.

A. Polymer Related Factors

a. Molecular Weight

Polymers usually diffuse into the mucosal layer and thereafter adhere to the layer by forming intermolecular entanglements. With the increase in the molecular weight (MW) of the polymer chain there is an increase in the mucoadhesiveness of a polymer. In general, polymers having MW $\geq$ 100, 000 have been found to have adequate mucoadhesive property for biomedical applications. A typical example is polyethylene glycol (PEG). PEG of 20,000 MW shows negligible mucoadhesive property while PEG of 200,000 MW exhibits improved mucoadhesiveness and the PEG of 400,000 MW has got excellent mucoadhesiveness. Similarly, polyoxyethylene of 7,000,000 MW has exhibited excellent mucoadhesive property and could be tried for the development of buccal delivery systems. Dextrans of 19,500,000 and 200,000 MW, poly (acrylic) acid of ~750,000 MW and polyethylene oxide of 4,000,000 MW also exhibit good bioadhesive property.

b. Flexibility of Polymer Chain Length

Polymer chain length plays an important role in bioadhesiveness. With the increase in the chain length of the polymers there is an increase in the mucoadhesive property of the polymer. Flexible polymer chains helps in the better penetration and entanglement of the polymer chains with that of mucosal layer thereby improving the bioadhesive property. The flexibility of the polymer chains is generally affected by the crosslinking reactions and the hydration of the polymer network. Higher the crosslinking density, lower is the flexibility of the polymer chains. Keeping this in mind, teethering of long flexible chains onto the polymer matrices, with high crosslinking density, appears to be an excellent idea to improve the bioadhesive property. In a recent study, this phenomenon was utilized to device tethered poly (ethylene glycol)–poly (acrylic acid) hydrogels with improved mucoadhesive properties. In addition to the reduced flexibility of the polymer chains, crosslinking results in the reduced diffusion of water into the crosslinked polymer matrix. But sufficient hydration of the polymer network is necessary for the complete opening of the interpolymeric pores within the polymer matrix in addition to the mobilization of the polymer chains.

Hence highly crosslinked polymeric matrix limits the interpenetration of polymer and mucin chains amongst themselves which in turn results in the decrease in the mucoadhesive strength. Apart from the MW and chain length of the polymer chains, spatial arrangement of the polymer chains may also play an important role. As mentioned above, dextrans of 19,500,000 and 200,000 MW exhibit good mucoadhesive properties. The efficiency of both dextrans and PEG (MW: 200,000) have been found to possess similar bioadhesive strength.

c. Functional Groups of the Polymer

Formation of hydrogen-bonds amongst the functional groups of the polymers and mucosal layer also plays an important role. In general, stronger the hydrogen bonding stronger is the adhesion. The functional groups responsible for such kind of interaction include hydroxyl, carboxyl and amino groups. Various polymers which have the ability to form strong hydrogen bonds include poly (vinyl alcohol), acrylic derivates, celluloses and starch. Apart from the hydrogen bond formation, the presence of functional groups within the polymer structure may render the polymer chains as polyelectrolytes. The presence of charged functional groups in the polymer chain has a marked effect on the strength of the bioadhesion and can be demonstrated by cell-culture-fluorescent probe technique.

Anionic polyelectrolytes have been found to form stronger adhesion when compared with neutral polymers.

d. Polymer Concentration

In addition to the above facts, the concentration of the polymer also plays a significant role in the process of mucoadhesion. At lower concentrations of the polymer chains, there is an inadequate and unstable interaction amongst the polymer and the mucosal layer resulting in poor mucoadhesive properties. In general, polymer concentration in the range of 1-2.5 wt % may exhibit sufficient mucoadhesive property for biomedical applications. However for certain polymers, like poly (vinyl pyrrolidone) and poly (vinyl alcohol), solvent diffusion into the polymer network decreases at very high polymer concentration due to the formation of the highly coiled structure thereby limiting interpenetration of the polymer and mucin chains with the subsequent reduction in the mucoadhesive property .

B. Environmental Factors

Apart from the above-mentioned physico-chemical properties of the polymeric network, various environmental factors also play an important role in mucoadhesion. As mentioned previously, mucoadhesive property is dependent on the presence of functional groups which can ionize so as to give a charge distribution on the polymer chains.

a. pH

The ionization of the functional group is dependent on the pH of the external medium. Hence, change in the pH of the external environment may play an important role in tailoring mucoadhesive property. As for example, chitosan (cationic polyelectrolyte) exhibit excellent mucoadhesive property in neutral or alkaline medium.

b. Applied Strength

To place a solid bioadhesive system, it is necessary to apply a defined strength. The adhesive strength increases with the applied strength or with the density of its application up to an optimum. The pressure initially applied to the mucoadhesive tissue contact site can affect the depth of interpenetration. If high pressure is applied for a satisfactory longer period of time polymers become mucoadhesive even though they do not have attractive interaction.

c. Contact Time

The contact time amongst the polymer matrix and the mucosal layer can also govern the mucoadhesive property. With the initial increase in the contact time there is an increase in the hydration of the polymer matrix and subsequent interpenetration of the polymer chains.

d. Secretion of the Model Substrate Surface

Since physical and biological changes may occur in the mucus gels on tissues under experimental conditions, the variability of biological substrate should be confirmed by examining properties like permeability, electrophysiology, or histology necessary before and after preparing the *in vitro* tests using tissues for the better *in vitro / in vivo* correlation.

e. Swelling

Swelling depends both on polymer concentration and on water presence. When swelling is too great, decrease in bioadhesion occurs; such phenomena must not occur too early, in order to exhibit to a sufficient action of the bioadhesive system.

C. Physiological Variables

The physiology of the mucosal layer may vary depending on the patho-physiological nature of the human body. The physiological factors which play an important role in governing the mucoadhesive property of a polymer matrix include texture and thickness of mucosa.

a. Mucin

The natural turnover of mucins molecules from the mucus layer is important for at least two reasons. First, the mucins turnover is expected to limit the residence time of the mucoadhesive on the mucus layer. No matter how high the mucoadhesive strength is. Mucoadhesives are detached from the surface due to mucin turnover. The turnover rate may be different in the presence of mucoadhesive. Second, mucin turnover results in substantial amount of soluble mucin molecules. These molecules interact with mucoadhesive before they have a chance to interact with mucus layer. Mucins turnover may depend on the other factors such as presence of blood. The calculated mucins turnover time is of 47-270 minutes. The ciliated cells in the nasal cavity are known to transport the mucus to the throat at a rate of

5mm/min. the mucociliary clearance in the tracheal region has been found.

b. Disease State

The physicochemical properties of the mucus are known to change during disease conditions such as common cold, gastric ulcers, ulcerative colitis, cystic fibrosis, bacterial and fungal infections of the female reproductive tract and inflammatory conditions of the eye. The exact structural changes taking place in mucus under these conditions are not clearly understood. If mucoadhesive are to be used in the diseased state, the mucoadhesive property under these conditions is not clearly understood. If mucoadhesives are to be used in the diseased state, the needs to be evaluated under it [27].

Polymers in Mucosal Drug Delivery

The polymers within this category are soluble in water. Matrices developed with these polymers swell when put into an aqueous media with subsequent dissolution of the matrix. The polyelectrolytes extend greater mucoadhesive property when compared with neutral polymers. Anionic polyelectrolytes, e.g. poly (acrylic acid) and carboxymethyl cellulose, have been extensively used for designing mucoadhesive delivery systems due to their ability to exhibit strong hydrogen bonding with the mucin present in the mucosal layer. Chitosan provides an excellent example of cationic polyelectrolyte, which has been extensively used for developing mucoadhesive polymer due to its good biocompatibility and biodegradable properties. Chitosan undergoes electrostatic interactions with the negatively charged mucin chains thereby exhibiting mucoadhesive property. The ionic polymers may be used to develop ionic complex with the counter-ionic drug molecules so as to have a drug delivery matrix exhibiting mucoadhesive property. Non-ionic polymers, e.g. poloxamer, hydroxypropyl methyl cellulose, methyl cellulose, poly (vinyl alcohol) and poly (vinyl pyrrolidone), have also been used for mucoadhesive properties. The hydrophilic polymers form viscous solutions when dissolved in water and hence may also be used as viscosity modifying/enhancing agents in the development of liquid ocular delivery systems so as to increase the bioavailability of the active agents by reducing the drainage of the administered formulations. These polymers may be directly compressed in the presence of drugs so as to have a mucoadhesive delivery system. Numerous polysaccharides and its derivatives like chitosan, methyl cellulose, hyaluronic acid, hydroxypropyl methylcellulose, hydroxypropyl cellulose, xanthan gum, gellan gum, guar gum, and carrageenan have found applications in ocular mucoadhesive delivery systems. Cellulose derivatives (e.g. cationic hydroxyethyl celluloses) have been used in conjunction with various anionic polymers for the development of sustained delivery systems.

1.Mucoadhesive delivery systems are being explored for the localization of the active agents to a particular location/ site. Polymers have played an important role in designing such systems so as to increase the residence time of the active agent at the desired location. Polymers used in mucosal delivery system may be of natural or synthetic origin.

Hydrogels

Hydrogels can be defined as three-dimensionally crosslinked polymer chains which have the ability to hold water within its porous structure. The water holding capacity of the hydrogels is mainly due to the presence of hydrophilic functional groups like hydroxyl, amino and carboxyl groups. In general, with the increase in the crosslinking density there is an associated decrease in the mucoadhesion.

Thiolated Polymers

The presence of free thiol groups in the polymeric skeleton helps in the formation of disulphide bonds with that of the cysteine-rich sub-domains present in mucin which can substantially improve the mucoadhesive properties of the polymers (e.g. poly (acrylic acid) and chitosan) in addition to the paracellular uptake of the bioactive agents. Various thiolated polymers include chitosan–iminothiolane, poly (acrylic acid)–cysteine, poly (acrylic acid)–homocysteine, chitosan–thioglycolic acid, chitosan–thioethylamidine, alginate–cysteine, poly (methacrylic acid)–cysteine and sodium carboxymethylcellulose–cysteine.

Lectin-based Polymers

Lectins are proteins which have the ability to reversibly bind with specific sugar / carbohydrate residues and are found in both animal and plant kingdom in addition to various microorganisms. Many lectins have been found to be toxic and immunogenic which may lead to systemic anaphylaxis in susceptible individuals on subsequent exposure. The specific affinity of lectins towards sugar or carbohydrate residues provides them with specific cyto-adhesive property and is being explored to develop targeted delivery systems. Lectins extracted from legumes have been widely explored for targeted delivery systems. The various lectins which have shown specific binding to the mucosa include lectins extracted from *Ulex europaeus* I, soybean, peanut and *Lens culinarius*. The use of wheat germ agglutinin has been on the rise due to its least immunogenic reactions, amongst available lectins, in addition to its capability to bind to the intestinal and alveolar epithelium and hence could be used to design oral and aerosol delivery systems[28].

Key attributes of polymer contributions to bioadhesion are:
1. Sufficient quantity of hydrogen bonding functional group (−OH and −COOH)
2 .High molecular weight and chain flexibility
3. Anionic surface charges.
4. Adequate surface tension to promote spreading into the mucus layer
5. Surface anchored groups with affinity to form bridges between polymer and mucin [29].

Methods for Mucoadhesion Measurement

Various *in vivo* and *in vitro* methods are used for testing the efficacy of the mucoadhesive nature of a polymer matrix. Commonly used *in vitro/ ex vivo* methods include tensile strength measurement, shear strength measurement and chip based systems whereas various imaging techniques are used for the evaluation of the delivery systems under *in vivo* conditions. This section will describe various methods used to study the mucoadhesive properties.

***In vitro* Tensile Strength Measurement**

In vitro tensile strength measurement is done by dipping a filter paper in 8% mucin dispersion. Thereafter, the mucin coated filter paper is placed in contact with the hydrated polymeric samples (in physiological solutions) for a definite period of time, followed by the determination of the maximum force required to detach the filter-paper and polymer surfaces after the mucoadhesive bonding.

***In vitro* Wash-off Test**

In vitro wash-off test may also be used to determine the mucoadhesive property of delivery systems. In the test, the mucosal tissue is attached onto a glass slide with the help of a double-sided cyanoacrylate tape. Thereafter, the delivery system is put on the surface of the tissue (exposed mucosal surface) with the subsequent vertical attachment of the system into the USP tablet disintegrator apparatus, which contains 1 L of physiological solution maintained at 37°C. The operation of the equipment gives an up-and-down movement to the tissue-delivery matrix system. In this study, the time for the complete detachment of the delivery system from the mucosal layer is determined.

***Ex vivo* Mucoadhesion Measurement**

Ex vivo experimentations are also done with the exception that the mucin coated filter-paper is replaced with excised mucosal tissues (e.g. buccal mucosa, intestinal mucosa, vaginal mucosa). The mucoadhesive properties can also be determined by incubating the hydrated polymer matrix surface kept in contact with a viscoelastic 30 % (w/w) mucin solution in water with the subsequent determination of the maximum detachment force required to separate the polymer matrix and mucin solution surfaces after the adhesion.

Modified Du Noüy Tensiometer

For the relative measurement of mucoadhesive nature of powder polymer samples modified Du Noüy tensiometer may be used, while in the shear strength determination method the force required to slide the polymer matrix over the mucus layer is determined.

BIACORE® Integrated Chip (IC) Systems

Recently mucoadhesion studies have been reported by using BIACORE® integrated chip (IC) systems. The method involves immobilization of the polymer (powder) on to the surface of the IC with the subsequent passage of the mucin solution over the same. This results in the interaction of the mucin with that of the polymer surface. The polymer-mucin interaction is measured by an optical phenomenon called Surface Plasmon Resonance (SPR), which measures the change in the refractive index when mucin binds on the polymer surface.

Gamma Scintiography Technique

The *in vivo* experiments involve the administration of radioactive labeled delivery system with the subsequent measurement of radioactivity in the tissues, at regular intervals of time, where the delivery system is supposed to adhere. The higher the radioactivity, the higher is the mucoadhesive property of the designed delivery system [30].

Advantages of Mucoadhesive Systems

There has been considerable interest in the field of mucoadhesive drug delivery systems since the immobilization of drug carrying particles at mucosal surface would result in:
1. Prolonged residence time at the site of drug action or absorption.
2. Localize action of drug molecule at a given target site.
3. An increase in the drug concentration gradient due to the intense contact of particles with the mucosal layer.
4. Direct contact with intestinal cells that is the first step before particle absorption [31].

Limitations

The continuous production of mucous by the mucosal membrane to replace the mucous that is lost through peristaltic contractions and the dilution of the GIT content limit the potential of mucoadhesive property [32].

Bioadhesive Multiparticulate Drug Delivery Systems

The oral route of drug administration constitutes the most convenient and preferred means of drug delivery to achieve systemic bioavailability. However oral administration of most of the drugs in conventional dosage forms has short-term limitations due to their inability to restrain and localize the system at gastrointestinal tract. In order to

circumvent this problem, it has been proposed successfully to associate drugs to polymeric particulate systems [33]. Carrier technology offers an intelligent approach for drug delivery by coupling the drug to a carrier particle such as microspheres, nanoparticles, liposomes, etc. which modulates the release and absorption characteristics of the drug [34]. Microspheres constitute an important part of these particulate drug delivery systems by virtue of their small size and efficient carrier capacity. However, the success of these microspheres is limited due to their short residence time at site of absorption. It would, therefore, be advantageous to have means for providing an intimate contact of the drug delivery system with the absorbing membranes. This can be achieved by coupling bioadhesion characteristics to microspheres and developing bioadhesive microspheres [35].

Techniques of Microparticles Preparation

For preparation of microparticles using biodegradable polymers, it is important to choose an appropriate encapsulation process which meets the following requirements.

- First, the chemical stability and biological activity of the incorporated drugs should be maintained during the encapsulation process. For example, since most proteins are readily denatured upon contact with hydrophobic organic solvents or acidic/basic aqueous solutions, the process should avoid such harsh environments.
- Second, the encapsulation efficiency and the yield of the microparticles should be high enough for mass production.
- Third, the microparticles produced should have the reasonable size range (< 250 μm) that can be administrated using the syringe needle via the parenteral pathway.
- Fourth, the release profile of the drug should be reproducible without the significant initial burst.
- Fifth, the process employed should produce free-flowing microparticles, thus making it easy to prepare uniform suspension of the microparticles.

There are a number of techniques available for microencapsulation of drugs such as the emulsion solvent evaporation/extraction method, spray drying, phase separation-coacervation, interfacial deposition, and *in situ* polymerization. Each method has its own advantages and disadvantages. The choice of a particular technique depends on the attributes of the polymer and the drug, the site of the drug action, and the duration of the therapy.

Emulsion-Solvent Evaporation/Extraction Methods

A. Single Emulsion Method

This method has been primarily used to encapsulate hydrophobic drugs through oil-in-water (o/w) emulsification process.

The polymer is dissolved in a water-immiscible, volatile organic solvent such as dichloromethane, and the drug is dissolved or suspended into the polymer solution. The resulting mixture is emulsified in a large volume of water in the presence of an emulsifier. The solvent in the emulsion is removed by either evaporation at elevated temperatures or extraction in a large amount of water, resulting in formation of compact microparticles. The rate of solvent removal is reported to affect the final morphology of microparticles. The solvent removal rate is determined by the temperature of the medium, the solubility characteristics of the polymer, and the solvent used. This method, however, is only available for the hydrophobic drugs because the hydrophilic drugs may diffuse out or partition from the dispersed oil phase into the aqueous phase, leading to poor encapsulation efficiencies. In an attempt to encapsulate hydrophilic drugs (e.g., peptides and proteins), an oil-in-oil (o/o) emulsification method has recently received considerable attention. In this method, the water miscible organic solvents are employed to dissolve the drug and polymer, whereas hydrophobic oils are used as a continuous phase of the o/o emulsion. The microparticles are obtained by removing the the organic solvents through evaporation or extraction process.

Double Emulsion Method

Most water-soluble drugs have been encapsulated by water-in-oil-in-water (w/o/w) methods.

The aqueous solution of the water-soluble drug is emulsified with polymer-dissolved organic solution to form the water-in-oil (w/o) emulsion. The emulsification is carried out using either high speed homogenizers or sonicators. This primary emulsion is then transferred into an excess amount of water containing an emulsifier under vigorous stirring, thus forming a w/o/w emulsion. In the subsequent procedure, the solvent is removed by either evaporation or extraction process. One advantage of this method is encapsulation of hydrophilic drugs in an aqueous phase with the high encapsulation efficiency. For this reason, the w/o/w emulsion system has been used widely for the development of protein delivery systems. The characteristics of the microspheres prepared by the double emulsion method are dependent on the properties of the polymer (such as composition and molecular weight), the ratio of polymer to drug, the concentration and nature of the emulsifier, temperature, and the stirring/agitation speed during the emulsification process [36].

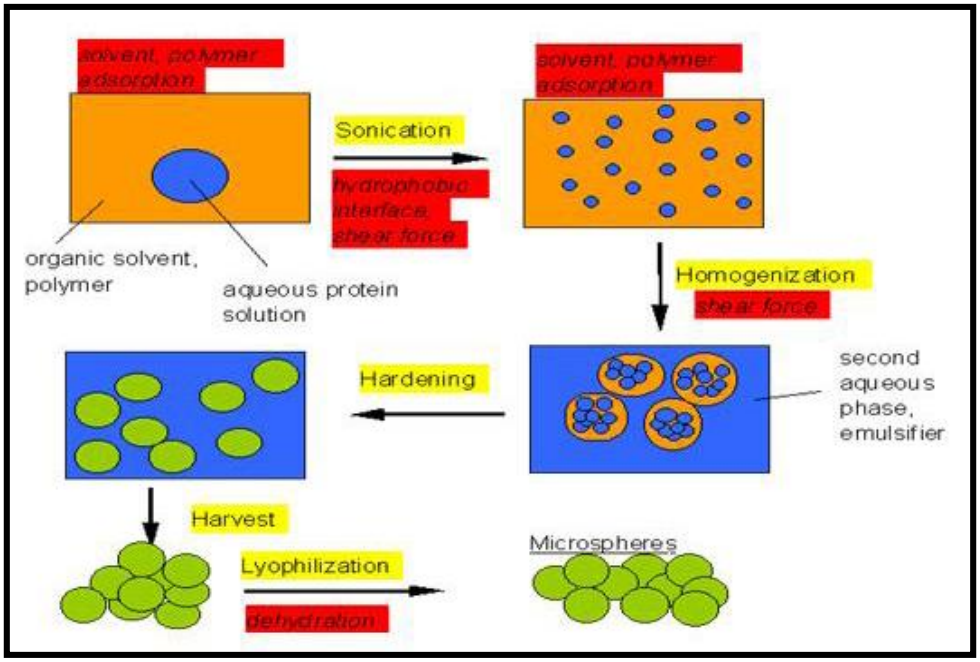

Fig 4: Solvent Evaporation Method [37]

C. Phase Separation

This method involves phase separation of a polymer solution by adding an organic non solvent. Drug is first dispersed or dissolved in a polymer solution. To this mixture

solution is added an organic nonsolvent (e.g., silicon oil) under continuous stirring, by which the polymer solvent is gradually extracted and soft coacervate droplets containing the drug are generated. The rate of adding nonsolvent affects the extraction rate of the solvent, the size of microparticles and encapsulation efficiency of the drug. The commonly used non solvents include silicone oil, vegetable oil, light liquid paraffin, and low-molecular-weight polybutadiene.

The coacervate phase is then hardened by exposing it into an excess amount of another nonsolvent such as hexane, heptane and diethyl ether. The characteristics of the final microspheres are determined by the molecular weight of the polymer, viscosity of the non solvent, and polymer concentration. The main disadvantage of this method is a high possibility of forming large aggregates. Extremely sticky coacervate droplets frequently adhere to each other before complete phase separation.

Recently, a novel method of preparing reservoir-type microcapsules, based on interfacial phase separation, was developed. Two different types of liquid droplets (i.e., a polymer solution and a drug solution) were separately produced using a dual microdispenser system consisting of two ink-jet nozzles, and the produced droplets were allowed to collide each other in the air. Upon collision, the drug-containing aqueous core remains spherical due to its high surface tension while the polymer-containing droplet spreads over the aqueous core. As a result, a reservoir-type microcapsule is generated due to the interfacial phase separation by the mutual mass transfer of two solvents (i.e., solvent exchange). Successful formation of microcapsules depends on the polymer concentration and the properties of the solvents, such as surface tension, interfacial tension, and the solvent exchange rate. This technique is promising for preparation of protein-loaded microcapsules. For example, conventional methods of preparing microparticles involve extensive exposure of proteins to the interface between aqueous and organic phases, to hydrophobic polymer matrix, and to acidic/basic microenvironments resulting from degradation of the polymer. These unfavorable interactions are reported to induce conformational changes of proteins. On the contrary, the interfacial phase separation technique is shown to minimize these sources of protein inactivation [38].

Miscellaneous

A. Thermal Cross-Linking

Chitosan (CS) solutions of varying concentration were prepared maintaining a constant molar ratio between CS and citric acid. The citric acid crosslinker solution was added then cooled at 0°C and added to corn oil followed by thermal crosslinking at 120°C.

B. Precipitation – Chemical Crosslinking

The Process involves the precipitation of the polymer followed by chemical cross linking. Precipitation can

be done by sodium sulphate followed by chemical crosslinking using glutaraldehyde. Aqueous solution of CS (3% (w/v) in 4% (v/v) glacial acetic acid) was added into agitating medium and stirring continued to obtain wet microspheres, which were then filtered, washed and finally dried at room temperature. The result show that solvent emulsification technique can also be used to prepare microspheres using heat as cross linking agent and avoiding the use of chemical as cross linking agent .

C. Ionotropic Gelation

The counter ions used for ionotropic gelation can be divided into 3 categories. Low molecular counter ions like pyrophosphate and tripolyphosphate, hydrophobic counter ions (e.g.: alginate k carrageenan), and high molecular weight ion (e.g. octyl sulphate, lauryl sulphate. The CS solution in acetic acid was extruded drop wise through a needle into different concentrations on aqueous solutions of magnetically stirred tripolyphosphate or some other an ion. The beads were removed from the counter ion solution by filtration washed with distill water and dried.

D. Wet Inversion

In this method of preparation chitosan solution in acetic acid was dropped in to an aqueous solution of counter ion sodium tripolyphosphate through a nozzle. Microspheres formed were allowed to stand for one hr washed and cross linked with 5% ethylene glycol di glysidyl ether. Finally the microspheres were washed and freeze dried to form porus CM. Changing the pH of the coagulation medium could modify the pore structure of CS.

E. Complex Coacervation

CS microparticles can also prepared by complex coacervation. Sodium alginate, sodium CMC k.Carregnan and sodium polyacrylic acid can be used for complex coacervation with CS to form microspheres. These microparticles are formed by interionic interaction between oppositely charged polymers solutions and KCl and $CaCl_2$ solutions [39].

F. Spray Drying[39]

Compared to other conventional methods, spray drying offers several advantages. It shows good reproducibility, involves relatively mild conditions, allows controlling the particle size, and is less dependent on the solubility of the drug and the polymer. In Spray drying, the polymer is first dissolved in a suitable volatile organic solvent such as dichloromethane, acetone, etc. The drug in the solid form is then dispersed in the polymer solution under high-speed homogenization. This dispersion is then atomized in a stream of hot air. The atomization leads to the formation of the small droplets or the fine mist from which the solvent evaporate instantaneously leading the formation of the microspheres in a size range 1-100µm. Microparticles are separated from the hot air by means of the cyclone separator while the trace of solvent is removed by vacuum drying. One of the major advantages of process is feasibility of operation under aseptic conditions. This process is rapid and this leads to the formation of porous microparticles shown in **Figure No. 5 [40]**.

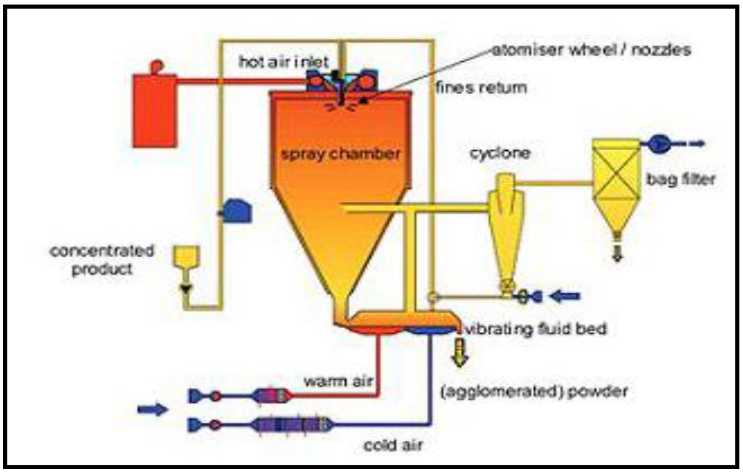

Fig 5: Spray dryer[41]

Applications of Bioadhesive Microspheres in Drug Delivery

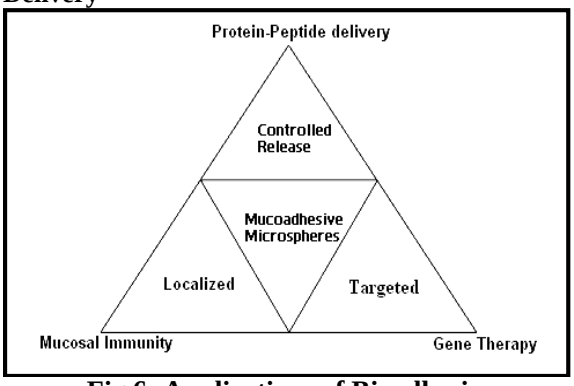

Fig 6: Applications of Bioadhesive Microspheres In Drug Delivery

Mucoadhesive microspheres have been extensively studied for a number of applications ("see **Figure No. 6**"). Majority of these can be understood by classifying these applications on the basis of routes of administration.

A) Topical Route

- Ocular drug delivery
- Nasal drug delivery
- Vaginal drug delivery

B) Oral Route

- Buccal drug delivery
- Gastrointestinal drug delivery
- Colon drug delivery

C) Miscellaneous

- Vesicular delivery
- Mucosal immunization
- Protein and peptide drug delivery [42]

Enteric- Coating of Mucoadhesive Microparticles

The intact molecule can be delivered to the small intestine without absorbing at the upper part of the intestine i.e. stomach environment by coating of the drug loaded microparticles molecule with the suitable polymers. The coating of pH-sensitive polymers to the mucoadhesive microparticles provide delayed release and the polymers used for lower GIT targeting, however, should be able to withstand the lower pH values of the stomach and of the proximal part of the small intestine and also be able to disintegrate at the neutral or slightly alkaline pH. These processes distribute the drug throughout the small intestine and improve the potential of targeted delivery systems[43].

Techniques of enteric-coating to microparticles

Various methods have been used for the preparation of microspheres are as follows:

A. Oil in Oil Solvent Evaporation Method

The dose of drug equivalent microspheres disperses in 10 mL of coating solution, prepared by dissolution of 500 mg of ES in ethanol: acetone (2:1). This organic phase is then pour in 70 mL of light liquid paraffin containing 1% wt/vol Span 85. The system is maintained under agitation speed of 1000 rpm at room temperature for 3 hours to allow for the evaporation of solvent. Finally, the coated microspheres filter & wash with n-hexane, and freeze-dried overnight [44].

B. Film Coating

The enteric coating solution is to be preparing by first making milky latex of Eudragit S100 using 1M ammonia (1.5%). After 1 hour TEC (60%) is added and stir for 30 minutes. Talc is then add to the milky latex as an antitacking agent. The enteric coating dispersion is passed through a 0.3-mm sieve before use. Throughout the coating process the coating dispersion is stir using a magnetic stirrer. The parameters of the film-coating process is as follows: pan rotating speed, 20 rpm; atomizing air pressure, 2 bar; inlet air temperature, 60 to 70-C; outlet air temperature, 35 to 40-C; bead bed temperature, 38-C. The film-coated beads are not remove from the pan until complete weight gain is achieved [45].

C. Solvent Removal Method

In this method, the dose equivalent of microbeads is dispersing in ethanolic solution of Eudragit L-100 and the mixture is stir at 500 rpm till complete removal of solvent occurs. Then it is filter and air dry. This process is repeat in triplicate [46] .

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