BIOADHESIVE SYSTEM

&

IN SITU GEL

Bioadhesive Systems

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1. INTRODUCTION

- Bioadhesion can be defined as a phenomenon of interfacial molecular attractive forces amongst the surfaces of the biological substrate and the natural or synthetic polymers, which allows the polymer to adhere to the biological surface for an extended period of time.
- 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.
- The use of mucoadhesive polymers for the development of pharmaceutical formulations dates back to 1947, when attempts were made to formulate a penicillin drug delivery system for delivering the bioactive agent to the oral mucosa using gum tragacanth and dental adhesive powders.
- Improved results were reported when carboxymethylcellulose and petrolatum were used for the development of the formulation. Subsequent

research resulted in the development of a mucoadhesive delivery vehicle which consisted of finely ground sodium carboxymethylcellulose (SCMC), pectin, and gelatin. The formulation was later marketed as Orahesive. Another formulation which entered into the clinical trials is Orabase, which is a blend of polymethylene/ mineral oil base.

- This was followed by the development of a system where polyethylene sheet was laminated with a blend of sodium carboxymethylcellulose and poly (isobutylene) which provided an added advantage of protecting the mucoadhesive layer by the polyethylene backing from the physical interference of the external environment.

- Over the years, various other polymers (e.g. sodium alginate, sodium carboxymethylcellulose, guar gum, hydroxyethylcellulose, karya gum, methylcellulose, polyethylene glycol (PEG), retene and tragacanth) have been found to exhibit mucoadhesive properties.
- During the period of 1980s poly (acrylic acid), hydroxypropylcellulose, and sodium carboxymethylcellulose were widely explored for the development of formulations having mucoadhesive properties.
- Since then the use of acrylate polymers for the development of mucoadhesive formulations have increased many-fold, various authors have investigated the mucoadhesive properties of different polymers with varying molecular architecture.
- After a lot of research, the researchers are of the view that a polymer will exhibit sufficient mucoadhesive property if it can form strong intermolecular hydrogen bonding with the mucosal layer, penetration of the polymer into the mucus network or tissue crevices, easy wetting of mucosal layer and high molecular weight of the polymer chain.
- The ideal characteristics of a mucoadhesive polymer matrix include the rapid adherence to the mucosal layer without any change in the physical property of the delivery matrix, minimum interference to the release of the active agent, biodegradable without producing any toxic byproducts, inhibit the enzymes present at the delivery site and enhance the penetration of the active agent (if the active agent is meant to be absorbed from the delivery site) Before discussing about the commonly used mucoadhesive polymers,

the different theories which have been proposed to explain the phenomenon of mucoadhesion will be discussed.

- Furthermore, different factors affecting mucoadhesion, methods of evaluation of mucoadhesive properties of polymers and the potential biological sites where mucoadhesion can play an important role will be taken up for discussion.

2. THEORIES OF MUCOADHESION

- The phenomena of bioadhesion occur 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) Electronic theory,
  (b) Wetting theory,
  (c) Adsorption theory,
  (d) Diffusion theory,
  (e) Mechanical theory and
  (f) Cohesive 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.
- 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.
- The 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.
- The diffusion theory assumes the diffusion of the polymer chains, present on the substrate surfaces, across the adhesive interface thereby forming a networked structure.

- The mechanical theory 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.
- 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) methods .

- The process of adhesion may be divided into two stages.
  - During the first stage (also known as contact stage), wetting of mucoadhesive polymer and mucous membrane occurs followed by the consolidation stage, where the physico-chemical interactions prevail .
  - As mentioned above, bioadhesion may take place either by physical or by chemical interactions.
  - These interactions can be further classified as hydrogen bonds, Van der Waals force and hydrophobic bonds which are considered as physical interactions while the formation of ionic and covalent bonds are categorized as chemical interactions.
  - Hydrogen bonds are formed due to the interaction of the electronegative and electropositive atoms though there is no actual transfer of electrons. Example of this kind of interaction includes formation of gelled structure when aqueous solutions of polyvinyl alcohol and glycine are mixed.
  - Van der Waals forces are either due to presence of the dipole-dipole interactions in polar molecules or due to the dispersion forces amongst non-polar substrates.
  - Hydrophobic bonds are formed due to the interaction of the non-polar groups when the polymers are dispersed in an aqueous solution. Freeze-thawing of polyvinyl alcohol solution in water exhibits this kind of interaction.
  - Ionic bonds are formed due to the electrostatic interactions amongst the polymers (e.g. instantaneous formation of gelled structure when alginate and

chitosan solutions in water are mixed) while covalent bonds are formed due to the sharing of electrons amongst the atoms (e.g. crosslinking reaction amongst genipin and amino groups).

- The term “mucoadhesion” was coined for the adhesion of the polymers with the surface of the mucosal layer.
  - The mucosal layer is made up of mucus which is secreted by the goblet cells (glandular columnar epithelial cells) and is a viscoelastic fluid. It lines the visceral organs, which are exposed to the external environment.
  - The main components constituting the mucosa include water and mucin (an anionic polyelectrolyte), while the other components include proteins, lipids and mucopolysaccharides.
  - Water and mucin constitute > 99% of the total composition of the mucus and out of this > 95% is water.
  - The gel-like structure of the mucus can be attributed to the intermolecular entanglements of the mucin glycoproteins along with the non-covalent interactions (e.g. hydrogen, electrostatic and hydrophobic bonds) which results in the formation of a hydrated gel-like structure and explains the viscoelastic nature of the mucus.

3. FACTORS AFFECTING MUCOADHESION

1. 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.

2. In this section, attempts will be made to analyze some of the parameters which can tailor the mucoadhesive property of a given polymer.Polymers usually diffuse into the mucosal layer and thereafter adhere to the layer by forming intermolecular entanglements.

3. 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 ≥ 100, 000 have been found to have adequate mucoadhesive property for biomedical applications.

4. 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.

5. 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.

6. 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.

7. 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.

8. 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 the dextrans and PEG (MW: 200,000) have been found to possess similar bioadhesive strength.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.

9. 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.

10. 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.

11. 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. 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.

12. 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.

4. EVALUATION OF MUCOADHESIVE PROPERTIES

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 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. Similarly, 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.
- 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 37^0C.
- 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. 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.
- 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.
- 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.

5. Targets for Bioadhesive Formulations

Bioadhesive or mucoadhesive formulations have been targeted to various anatomical locations to aid drug delivery and absorption. These structures possess mucous membranes which protect the cell from damage. Drug delivery to each anatomical region is discussed below.

Table 1: Sites to which bioadhesive formulations are targeted

Body site	Systems
Eye	Mucoadhesive eye drops / inserts
Nasal cavity	Nasal drug delivery systems
Oral cavity	Dental gels / buccal systems
Skin	Patches, tapes, dressings
Vagina	Local vaginal delivery systems
Rectum	Local/systemic rectal delivery systems

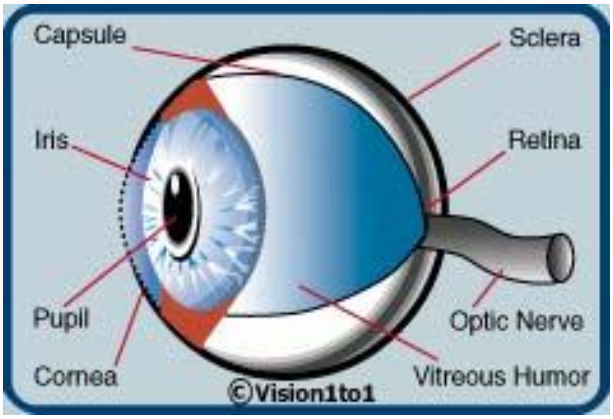
Targets for Bioadhesive Formulations

The eye

The eye is one of the most important and complex organs of the body, because of its complicated anatomy many things can go wrong with the eye. Topical drug delivery systems to the eye can be very difficult to achieve because the eye has several protective mechanisms in place to get rid of foreign substances**.**

An effective ocular drug delivery system must be easy to use, comfortable to the patient and maintain substantial concentrations of the drug in the eye to produce therapeutic effects.

A brief anatomy of the eye



Some conditions of the eye

- **Conjunctivitis** – This is an inflammation of the conjunctivae, which are mucous membranes covering the whites of the eye and the inside of the eyelids. It is caused by bacteria, viruses or allergens and the signs and symptoms displayed by the patient will be dependent on the type of conjunctivitis. The symptoms include: redness of the eye, grittiness or itchy eyes and the presence of a sticky or watery discharge.
- **Dry eye** – This occurs when people don't have enough tears or the adequate composition of tears required to lubricate the eyes. The occurrence of dry eye increases with age and is therefore common in older people. The eyes become itchy, gritty, painful and have a burning sensation.
- **Glaucoma** – This disorder is characterised by pressure in the eyeballs and causes excessive amounts of aqueous humour (the fluid that fills the eyeballs). This puts pressure on the optic nerves and compresses the blood vessels in the eye. The resultant effects include abnormalities in vision and total blindness.

Ocular Bioadhesive Formulations

- GelTears® and Viscotears® Liquid gel eye drops are used for dry eye conditions and contain carbomer 980 (polyacrylic acid). Carbomers lubricate the eye by clinging to the surface of the eye. This can help reduce the frequency of their application into the eye.

- Pilogel® is an eye gel used in the treatment of glaucoma. It contains the high molecular weight polymer polyacrylic acid. The polymer increases the viscosity of the gel which provides a prolonged retention of the gel in the eye.

The Nasal Cavity

- The nasal cavity is the air passage behind the nose. This is the source of the moisture which is added to air during the breathing process. The nasal cavity has a complex structure and can become inflamed during conditions such as the common cold, nasal allergies and flu.
- Drugs such as antihistamines and steroids are administered as nasal drops or nasal sprays to treat conditions affecting the nose. However nasal mucociliary clearance affects the retention and therefore the effects of the drugs in the nose. Mucociliary clearance transports mucus from the cells lining the nose and protects the respiratory tract from damage caused by inhaled substances including dirt particles and medicines.

Nasal Bioadhesive Formulations

- By mixing drugs targeted for the nose with bioadhesive polymers, the process of mucociliary clearance of the drug can be overcome. The effects of bioadhesive polymers on mucociliary clearance were examined by **Zhou and Donovan (1996).** All the polymers examined showed decreases in mucociliary clearance. Methylcellulose exhibited the most reduction in mucociliary clearance whilst Carbopol 934P showed the least reduction in mucociliary clearance in the rats used.

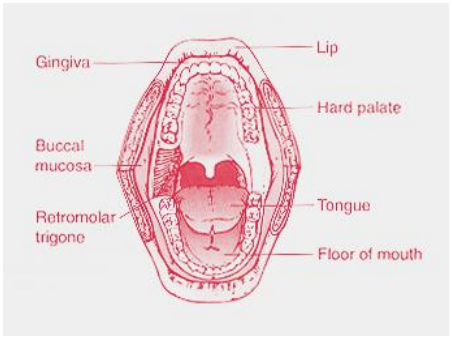
EXAMPLES OF PRODUCTS

- **Rhinocort®** Nasal spray is a powdered mixture of the steroid Beclomethasone dipropionate(50µg) and 30mg of Hydroxypropyl cellulose(HPC). Patients suffering from nasal allergy administer one spray twice a day into the nasal cavity.The powder sticks to and swells on the cells lining the nose and remains there until approximately six hours after administration.

- **Beconase®** Nasal spray is used to treat nasal inflammation and nasal allergies associated with hayfever. It contains the active ingredient Beclometasone dipropionate and the bioadhesive polymers carboxymethyl cellulose and microcrystalline cellulose.
- **Nasacort®** Nasal spray is used to treat allergies that result in inflammation of the nose. The active ingredient in this product is Triamcinolone acetonide as well as the bioadhesive polymer microcrystalline cellulose. The polymer swells in the presence of water and is able to spread across the nasal mucosa thus helping the distribution of the drug over the mucosal surface.

The oral cavity

The oral cavity or the mouth comprises of the cheeks, hard and soft palates and the tongue. It is an entrance of the digestive system and plays many important functions which include chewing, speaking and tasting. Some of these functions are impaired by diseases such as ulcers, microbial infections and inflammation.



Common conditions affecting the oral cavity

- **Mouth ulcers**: A mouth ulcer can be described as a breach or break in the mucous membrane that lines the inside of the mouth. The majority of patients

suffer from minor aphthous ulcers (MAU). These ulcers are roundish, shallow, grey-white in colour and are painful. They are small and appear in small crops.

- **Oral thrush**: This is an infection caused by the fungus *Candida albicans* in the oral cavity. It can also arise due to risk factors such as diabetes, recent antibiotic therapy and inhaled corticosteroids. Oral thrush presents itself as soft creamy-white patches which can be wiped off. The lesions are painful and can occur anywhere in the oral cavity.
- **Gingivitis**: Gingivitis means inflammation of the gums. It is caused by the build-up of plaque (a layer of bacteria) on the teeth. The gums become reddened, swollen and bleed easily with slight trauma such as brushing the teeth.

Oral Bioadhesive Formulations

Oral bioadhesive formulations are topical products designed to deliver drugs to the oral cavity which act by adhering to the oral mucosa and therefore produce localised effects within the mouth.

EXAMPLES OF PRODUCTS

Corlan®- Corlan pellets are used in the treatment of mouth ulcers to reduce the pain, swelling and inflammation associated with mouth ulcers. The active ingredient of the pellet is Hydrocortisone succinate. It also contains the bioadhesive polymer *Acacia* which helps prolong the effect of the drug in the oral cavity. For treatment to be successful each pellet or lozenge must be allowed to slowly dissolve in the mouth, close to the ulcer.

A. The Buccal Mucosa

The buccal mucosa refers to the inner lining of the lips and cheeks. The epithelium of the buccal mucosa is about 40-50 cells thick and the epithelial cells become flatter as they move from the basal layers to the superficial layers.

The buccal mucosa is less permeable compared to other oral drug delivery systems and is unable to retain dosage forms at the site of absorption. The use of bioadhesive polymers in buccal drug delivery systems allows a better retention of a dosage form by spreading it over the absorption site.

Examples of Products

- **Buccastem®** Is a drug used in the treatment of nausea, vomiting and vertigo. It contains the bioadhesive agents Polyvinylpyrrolidone and Xanthan gum.
- **Suscard®** Is a buccal tablet used in the treatment of angina. It contains the bioadhesive agent Hydroxypropyl methylcellulose (HPMC).

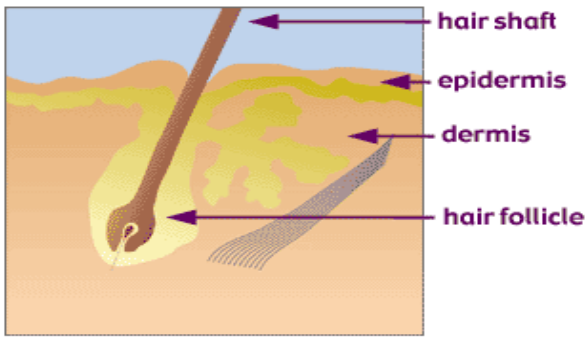
B. The sublingual mucosa

- The sublingual mucosa surrounds the sublingual gland which is a mucin-producing salivary gland located underneath the tongue.
- This mucosa is relatively permeable and gives a rapid absorption of many drugs due to its excellent blood supply. The sublingual route of drug delivery is convenient, accessible and generally well accepted by patients.
- Drugs administered via the sublingual route are formulated as tablets, powders, solutions or aerosol sprays. This route is appropriate for many drugs as long as the drug is able to go into solution with saliva in the mouth.
- Examples of sublingual products include **Glyceryl Trinitrate (GTN**) aerosol spray and tablet which is administered under the tongue for the prophylactic treatment of angina.

The Skin

The skin is the outer covering of the body and consists of different layers. It performs several functions which include:

- Protecting the body from injury and invasion by pathogens
- Preventing the body from becoming dehydrated
- Regulating body temperature
- Production of Vitamin D



Topical Bioadhesive Formulations

The drug delivery systems used in this case are required to adhere to the skin for the purpose of:

- ❖ Collecting body fluids
- ❖ Protecting the skin
- ❖ Providing local or systemic drug delivery

Adhesion can be described as the formation of a new mechanical bond between the skin and the adhesive agent. Bioadhesive products targeted to the skin are formulated into different dosage forms which include liquids, powders and semi-solids such as ointments and transdermal patches.

Transdermal patches are sustained-release devices that release a specific amount of drug whilst firmly attached to the skin. They must provide a firm, soft contact with the skin but also allow the patch to be easily removed with minor effort.

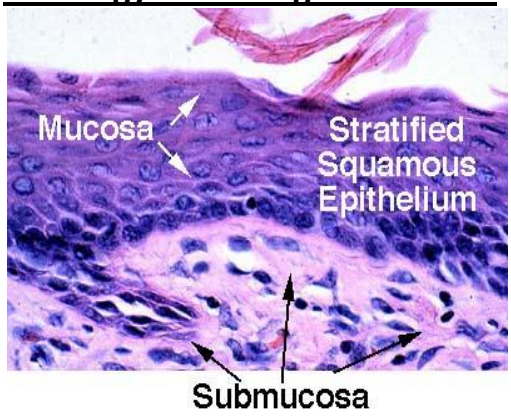
Examples of Products

- **Voltarol Emulgel:** This is a gel which provides a local relief from pain and inflammation in the tendons, muscles and joints. It contains the bioadhesive polymer carbomer which aids the absorption of the active drug by spreading it into the affected area.
- **Feldene:** This gel is used in the treatment of conditions which are characterised by pain, inflammation and stiffness. The active ingredient in this formulation is piroxicam but the gel also contains two bioadhesive agents to increase its retention at the absorption site. These agents are Carbopol 980 and hydroxyethyl cellulose.

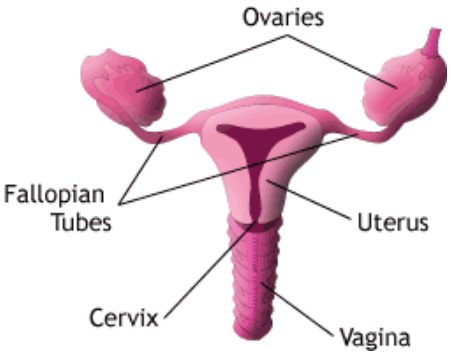
The Vagina

The vagina is the lower part of the female reproductive tract. It is a muscular tube lined with mucous membrane which is covered with a layer of stratified squamous epithelium with an underlying layer of connective tissue (lamina propria).

Histology of the vaginal mucosa



The female reproductive System



Common conditions affecting the vagina

The epithelium of the vagina contains glycogen, which is broken down enzymes and bacteria into acids such as lactic acid. This maintains a low vaginal pH which is normally between 4 and 5. Such a pH is desirable because it makes the vagina in hospitable to pathogens. Decreased levels of glycogen in the vagina leads to an increase in vaginal pH and makes the vagina more susceptible to infection.

Common vaginal infections

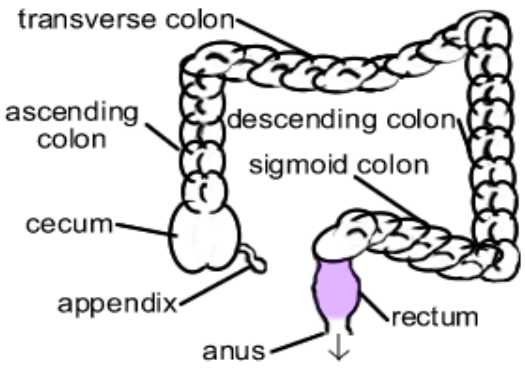
- **Vaginitis:** Vaginitis means inflammation of the vagina and it creates discharge, odour, irritation or itching. It has many causes which includes infection with Trichomonas vaginalis, dietary deficiency or poor hygiene.
- **Bacterial vaginosis:** The causal organism often implicated in this infection is Gardnerella vaginalis, although other bacteria present in the vagina also contribute to the cause. The infection arises due to the overgrowth of these bacteria. About 50% of patients will have a thin white discharge with a strong fishy odour.
- **Candidiasis (Thrush):** Is a common yeast infection caused by the organism Candida albicans. The signs and symptoms of thrush are a white cheesy discharge that itches and irritates the vagina.
- **Trichomoniasis:** Is a sexually - transmitted infection caused by the organism Trichomonas vaginalis. The symptoms in women include vaginal itching as well as a frothy, foul-smelling, greenish-yellow discharge**.**

Vaginal bioadhesive formulations

- The intravaginal route has been used to deliver contraceptives as well as anti-infective agents such as antifungal drugs to exert a local effect. Agents targeted for the vaginal route have been formulated into various dosage forms including creams, gels and vaginal tablets.
- Localised application of vaginal formulations enables the spread of these formulations over the target area, which allows an effective therapy.
- Bioadhesive polymers are incorporated into vaginal formulations to aid the adhering of the dosage form to its target site. Polymers also increase the retention of the active drug in the vagina and also optimise the spread of the formulation over the vaginal epithelium.

The Rectum

The rectum is the terminal or end portion of the gastrointestinal tract. It is an important route of administration for drugs that have severe gastrointestinal side effects. This route is also suitable for patients who cannot take medicines via the oral route such as unconscious patients and infants. The drugs absorbed from the rectum can escape breakdown by hepatic enzymes. For this reason mucoadhesive suppositories have been developed for the local treatment of diseases such as haemorrhoids and rectal cancer.



Rectal Bioadhesive Formulations

Bioadhesive polymers are incorporated into rectal suppositories to prolong the retention of the active drug in the rectum. Prolonged retention in the rectum increases the chances of reaching a therapeutic outcome.

EXAMPLES OF PRODUCTS

- **Anacal®** is a rectal ointment used to relieve the symptoms associated with haemorrhoids. It contains the bioadhesive agent polyethylene high polymer 1500.
- **Germoloids®** is a rectal ointment used to relief the pain, swelling, itchiness and irritation associated with haemorrhoids. It contains the polymer propylene glycol.

Preparation H® Suppositories help shrink the haemorrhoidal tissue which is swollen by irritation. It contains the polymer polyethylene glycol

IN SITU GEL

Introduction

The use of preformed gels has suffers some drawbacks that can limit their interest for rectal drug delivery. They do not allow easy, accurate, and reproducible administration of formulation. A new concept of producing an *in situ* forming gel formulation was suggested.

Compared to conventional controlled release formulations, *in situ* forming drug delivery systems possess potential advantages. Benefits include simple manufacturing processes and ease of administration. The vast majority of the *in situ* forming drug delivery systems reported is based on polymeric materials which forms gel matrices upon administration. Polymers that have been investigated includes (1) polysaccharides like alginate, gellan and xyloglucan, (2) polyesters like PLA and PLGA, (3) polyethers like PEG-PPG-PEG (Poloxamers) or (4) mixed polyesters and polyethers such as PEG-PLGA-PEG.

The new approach helps to achieve combined advantages of both solutions and gels, such as ease of administration of the former and prolonged residence time of the latter. The *in situ* forming gel formulation can provide controlled release of API for prolonged period of time.

The stimuli that induce various responses of the hydrogel systems include physical (temperature, electric fields, light, pressure, sound, magnetic fields), chemical (pH, ions) or biological/ biochemical (biomolecules) ones. Based on different stimuli, *in situ* forming hydrogels can be classified as follow:

1. Temperature-sensitive hydrogels
2. pH-sensitive hydrogels
3. Ion-sensitive hydrogels
4. Dilution-sensitive hydrogels
5. Electrical signal-sensitive hydrogels
6. Light-sensitive hydrogels
7. Glucose-sensitive hydrogels

1. Temperature-Sensitive Hydrogels

Temperature is one of the most widely used stimuli for stimuli-sensitive hydrogels, because it is easy to control and has practical advantages both in vitro and in vivo. These formulations are liquid at room temperature (20-25°C) and undergo gelation when comes in contact with application site (35-37°C), due to an increase in temperature. Temperature-sensitive hydrogels undergo a volume phase-transition or a sol–gel phase-transition at a critical temperature, namely, lower critical solution temperature (LCST) or upper critical solution temperature (UCST).

The LCST polymers exhibit a hydrophilic-to-hydrophobic transition with increasing temperature, whereas the UCST systems undergo the opposite transition. In contrast to the UCST systems, the LCST systems have received more attention for drug delivery because mixing of the UCST systems and drugs needs to be performed at relatively high temperature, which may be harmful to some unstable drugs or biomolecules and bring inconvenience into the drug formulation.

Typical LCST polymers include poly(N-isopropylacrylamide) (PNIPAM), poly(N,N-diethylacrylamide) (PDEAM), poly(vinyl ether) (PVE), poly(N-vinylalkylamide) (PNVAAM), poly(N-vinylcaprolactam) (PNVCa), polyphosphazene derivatives and poly(N-(2-hydroxypropyl) methacrylamide mono/di lactate) (PHPMAM-mono/dilactate).

Poloxamers are the most commonly used thermosetting polymers in *in-situ* gel forming drug delivery. Depending on the ratio and the distribution along the chain of hydrophobic and hydrophilic subunits, several molecular weights are available, leading to different gelation properties. Lutrol F-127 and Lutrol F-68, which give colorless and transparent solution, are the most commonly used polymers in various drug delivery systems.

Three principle mechanisms have been proposed to explain the sol-to-gel transition after an increase in temperature.

1. Gradual dissolvation of the polymer,
2. Increased micellar aggregation, and
3. The increased entanglement of the polymeric network.

Ultrasonic velocity, light-scattering and small-angle neutron scattering measurements of aqueous poloxamer solutions have clearly indicated a micellar mode of association. Micelle formation occurs at the critical micellization temperature as a result of PPO (Poly(Propylene Oxide)) block dehydration. Temperature increase and, as a result, dehydration of polymer chains leads to the formation of hydrophobic domains and eventually transition of an aqueous liquid to a hydrogel network. With increasing temperature, micellization becomes more important, and at a definite point, micelles come into contact and no longer move. In addition, the formation of highly ordered structures, such as cubic crystalline phase, has been proposed as the driving force for gel formation, but this hypothesis has been questioned recently.

Thermo reversible gels can be prepared with naturally occurring polymers. Most natural polymer aqueous solutions form a gel phase when their temperature is lowered. Classic examples of natural polymers exhibiting a sol–gel transition include gelatin and carrageenan. At elevated temperatures, these polymers adopt a random coil conformation in solution. Upon cooling, a continuous network is formed by partial helix formation.

Some cellulose derivatives are an exception to this gelation mechanism. At low concentrations (1–10 wt. %), their aqueous solutions are liquid at low temperature, but gel upon heating. Methylcellulose (Fig. 4a) and hydroxypropyl methylcellulose (HPMC) (Fig. 4b) are typical examples of such polymers.

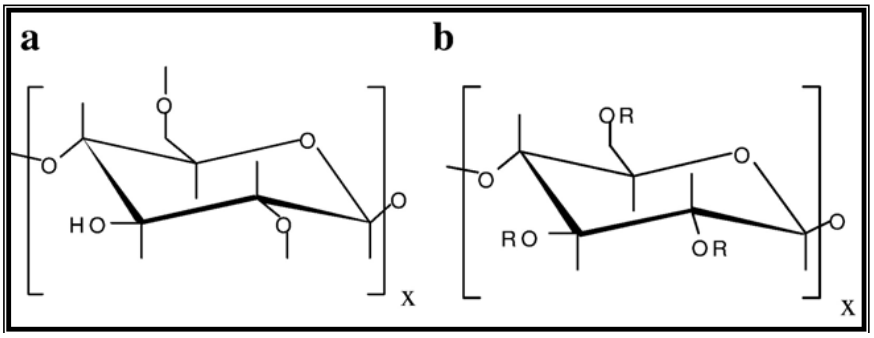


Fig: Structure of (a) Methylcellulose (MC) (b) Hydroxypropylmethylcellulose (HPMC) R=CH_3 or CH_2 CH (CH_3) OH or H

Methylcellulose solutions transform into opaque gels between 40 and 50 °C, whereas HPMC shows phase transition between 75 and 90 °C. These phase

transition temperatures can be lowered by chemical or physical modifications. For example, NaCl decreases the transition temperature of methylcellulose solutions to 32–34 °C. Similarly, by reducing the hydroxypropyl molar substitution of HPMC, its transition temperature can be lowered to 40 °C.

2. pH-Sensitive Hydrogels

pH is another important environmental parameter for drug delivery systems, because the pH change occurs at many specific or pathological body sites, such as stomach, intestine, endosome, lysosome, blood vessels, vagina and tumor extracellular sites.

These formulations are polymeric dispersion in aqueous system which undergoes spontaneous gelation in response to change in pH after application at the target site. Generally the ionic polymers like polyacrylamide (PAAM), poly (acrylic acid) (PAA), and poly (methacrylic acid) (PMAA) are used for the preparation of pH sensitive hydrogels.

All the pH-sensitive polymers contain pendant acidic or basic groups that either accept or release protons in response to changes in environmental pH. Swelling of hydrogel increases as the external pH increases in the case of weakly acidic (anionic) groups, but decreases if polymer contains weakly basic (cationic) groups. The choice of polymer is determined by its compatibility with API, stability and its ability to give a free-running solution at formulation pH.

3. Ion-Sensitive Hydrogels

In this type of *in situ* hydrogels, the sol-to-gel transition is induced by the presence of mono or divalent cations such as Na^{+}, K^{+}, Ca^{++}, and Mg^{++} ions. Naturally occurring anionic polymers like gellan Gum, sodium alginate, carragenan, and xyloglucans are having the characteristics property of cationic-induced gelation. Gellan gum commercially available as Gelrite® is an anionic polysaccharide that undergoes in situ gelling in the presence of mono- and divalent cations, including Ca^{2+}, Mg^{2+}, K^{+} and Na^{+}. Some other parameters influence the phase transition, i.e.

Concentration of polysaccharides, temperature of preparation, and the nature and concentration of cations.

4. Dilution-Sensitive Hydrogels

This type of hydrogel contains polymer that undergoes phase transition in presence of higher amount of water. By having a system undergoing phase transition as a consequence of dilution with water a higher amount of polymer can be used. The Lutrol F68–water–LP–Akoline MCM system shows an interesting phase behavior with the presence of a low-viscous isotropic region that turns into a hexagonal phase as the water content increases. The viscosity and elastic modulus of the isotropic phase is low whereas that of the hexagonal phase is high, the difference between the phases being 1000- to 10,000-folds. The viscosity increase is essentially independent of temperature in the temperature range of 20–37°C, but strongly dependent on the water content.

5. Electrical Signal-Sensitive Hydrogels

Hydrogels sensitive to electric current are usually made of polyelectrolytes such as the pH-sensitive hydrogels. Electro-sensitive hydrogels undergo shrinking or swelling in the presence of an applied electric field. Chitosan gels as matrices can be used for electrically modulated drug delivery. In electrification studies, release-time profiles for neutral (hydrocortisone), anionic (benzoic acid) and cationic (lidocaine hydrochloride) drug molecules from hydrated chitosan gels were monitored in response to different milliamperages of current as a function of time. Likewise, chondroitin 4-sulphate hydrogels can be used as potential matrices for the electro-controlled delivery of peptides and proteins.

6. Light-Sensitive Hydrogels

Light-sensitive hydrogels can be used in the development of photo-responsive artificial muscle or as the *in situ* forming gels for cartilage tissue engineering. Hydrogels that may undergo transdermal photopolymerization after subcutaneous injection were found to be applicable as drug delivery devices. Novel tissue adhesive technology based on photocrosslinkable gelatin, which allows *in*

situ drug-incorporated gelatinous gel formation on diseased tissue and sustained drug release is developed. *In situ* photopolymerizable hydrogel systems for barriers and local drug delivery in the control of wound healing were also studied.

7. Glucose-Sensitive Hydrogels

Intelligent stimuli-responsive delivery systems using hydrogels that can release insulin have been investigated. Cationic pH-sensitive polymers containing immobilized insulin and glucose oxidase can swell in response to blood glucose level releasing the entrapped insulin in a pulsatile fashion. Another approach is based on competitive binding of insulin or insulin and glucose to a fixed number of binding sites in concanavalin A, where insulin is displaced in response to glucose stimuli, thus functioning as a self-regulating insulin delivery system. An alternative route through phenylborate-poly(vinyl alcohol) polymers is also possible.

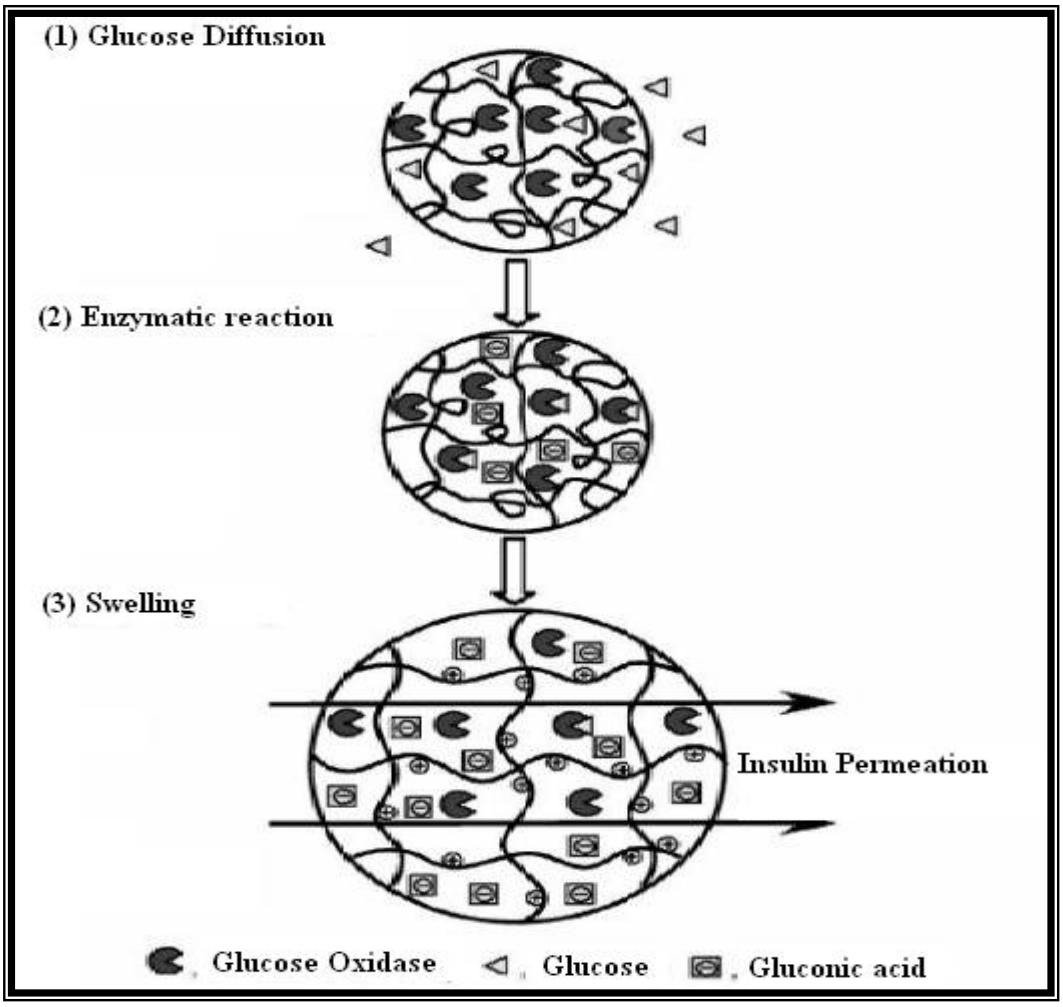


Fig: Glucose Sensitive Hydrogel

Their highly porous structure can easily be tuned by controlling the density of cross-links in the gel matrix and the affinity of the hydrogels for the aqueous environment in which they are swollen. Their porosity also permits loading of drugs into the gel matrix and subsequent drug release at a rate dependent on the diffusion coefficient of the small molecule or macromolecule through the gel network. Indeed, the benefits of hydrogels for drug delivery may be largely pharmacokinetic especifically that a depot formulation is created from which drugs slowly elute, maintaining a high local concentration of drug in the surrounding tissues over an extended period, although they can also be used for systemic delivery.

Polymers Used In Hydrogel Fabrication

Hydrogels can be prepared from natural or synthetic polymers. Although hydrogels made from natural polymers may not provide sufficient mechanical properties and may contain pathogens or evoke immune/ inflammatory responses, they do offer several advantageous properties such as inherent biocompatibility, biodegradability, and biologically recognizable moieties that support cellular activities. Synthetic hydrogels, on the other hand, do not possess these inherent bioactive properties. Fortunately, synthetic polymers usually have well-defined structures that can be modified to yield tailorable degradability and functionality.

Table: Natural polymers and synthetic monomers used in hydrogel fabrication

Natural polymers	Synthetic monomers
✓ Chitosan ✓ Alginate ✓ Fibrin ✓ Collagen ✓ Gelatin ✓ Dextran ✓ Hyaluronic acid ✓ Gellan gum	✓ Hydroxyethyl methacrylate (HEMA) ✓ N-(2-hydroxypropyl) methacrylate (HPMA) ✓ Poly(ethylene oxide)-poly(propylene oxide)-poly (ethylene oxide) ✓ N-vinyl-2-pyrrolidone (NVP) ✓ Hyaluronic acid Acrylic acid (AA) ✓ Vinyl acetate (VAc) ✓ Methacrylic acid (MAA) ✓ Polyethylene glycoacrylate /methacrylate(PEGA/PEGMA)

DESIGN CRITERIA FOR HYDROGELS IN DRUG DELIVERY

Materials selection and network fabrication governs the rate and mode of drug release from hydrogel matrices. Several design criteria are crucial for drug delivery formulations and have to be evaluated prior to hydrogel fabrication and drug loading. These criteria are also important in mathematical modeling of drug release. Table 2 lists these important criteria and variables for designing hydrogel-based drug carriers.

Table: Design criteria for hydrogels in drug delivery formulations

Design properties	Design variables
Transport properties Molecule diffusion	• Molecular weight and size of protein • Molecular weight of polymer • Crosslinking density • Polymer–protein interactions • Hydrogel degradation rate • Additional functionalities
Physical properties Gelling mechanisms /conditions Structural properties Biodegradability Stimuli-responsiveness	• Polymer/crosslinker/initiator concentrations • Temperature, pH, ionic strength • Molecular weight of polymer • Mechanical strength • Concentration of degradable groups • Concentration of responsive groups
Biological properties Biocompatibility	• Cytotoxicity of the hydrogel • Capsule formation

APPLICATIONS OF HYDROGELS IN DRUG DELIVERY

A. Parenteral Delivery

One of the most obvious ways to provide sustained release medication is to place the drug in a delivery system and inject or implant the system into the body tissue. Thermoreversible gels mainly prepared from poloxamers are predominantly used. The suitability of poloxamer gel alone or with the addition of hydroxypropylmethylcellulose (HPMC), sodium carboxy- methylcellulose or dextran was studied for epidural administration of drugs *in vitro*. The compact gel depot acted as the rate-limiting step and significantly prolonged the dural permeation of drugs in comparison with control solutions.

Pluronic F127 gels which contained either insulin or insulin-PLGA nanoparticles can be useful for the preparation of a controlled delivery system. [48] Likewise, poloxamer gels were tested for intramuscular and subcutaneous administration of human growth hormone or with the aim to develop a long acting single dose injection of lidocaine.

A new class of injectable controlled release depots of protein which consisted of blends of Pluronics with poly(D, L-lactide)/1-methyl- 2-pyrrolidone solutions is developed. Some other thermosensitive hydrogels may also be used for parenteral administration. ReGel® (triblock copolymer PLGA-PEG-PLGA) was used as a drug delivery carrier for the continuous release of human insulin. Steady amounts of insulin secretion from the ReGel® formulations up to day 15 were achieved after subcutaneous injections.

The synthesis of a biodegradable poly(ethylene oxide) and poly(L-lactic acid) hydrogel, which exists in a form of sol at an elevated temperature (around 45°C) and forms a gel after subcutaneous injection and subsequent rapid cooling to body temperature is also studied.

Novel thermosensitive combinations of chitosan/polyol salts, which turn into gel implants when injected *in vivo* were developed. These formulations may be prototype for a new family of thermosetting gels highly compatible with biological compounds. Hydrogels formed by xyloglucan were also evaluated as a sustained

release vehicle for the intraperitoneal administration of mitomycin. PAA/polymethacrylic acid forms a pH-sensitive complex with PEG *in situ*, possessing the potential to release drug substances subcutaneously over a period of a few days. Alternatively, an aqueous solution containing MC in combination with polymethacrylate yields a reversible gel due to the change of temperature and pH shortly after parenteral administration.

B. Ocular Delivery

The efficacy of ophthalmic hydrogels is mostly based on an increase of ocular residence time via enhanced viscosity and mucoadhesive properties. Since resulted swollen hydrogel is aqueous based, it is very comfortable in the human eye. Among these polymers, *in situ* gels are preferred since they are conveniently dropped in the eye as a solution, where undergo transition into a gel. Thermosensitive, specific ion sensitive or pH-sensitive hydrogels have been examined for their potential as vehicles for ocular drugs.

Poloxamers as thermogelling polymers could be applicable for the development of effective ophthalmic drug delivery. In order to reduce the concentration of polymer and/or to achieve a phase transition temperature higher than room temperature (25°C) and gelling at precorneal temperature (35°C), the combining Pluronic® analogues or the addition of further polymer, e. g. PEG , PAA , methylcellulose (MC), HPMC, CMC is often necessary. An alternative *in situ* gelling material of natural origin, xyloglucan, was evaluated for the sustained ocular delivery of pilocarpine and timolol .

Ion-sensitive polymers belong to the mainly used *in situ* gelling materials for ocular drug delivery. Slightly viscous gellan gum solutions in low concentrations (<1%) show markedly increase in apparent viscosity, when introduced into presence of a physiological level of cations, without requiring more ions than 10–25% of those in tear fluid. The precorneal contact times for drugs can thus be extended up to 20-h. Gellan containing formulations of pilocarpine HCl allowed reduction of drug concentration from 2% to 0.5% obtaining the same bioavailability. The ability of gel formation at physiological Ca^{2+} levels was used in case of alginic acid as well. Presence of this polymer significantly extended the

duration of the pressure reducing effect of pilocarpine to 10-h and carteolol to 8-h allowing only once a day administration in case of carteolol.

Aqueous solutions of PAA that transform into gels upon increase in pH may be used as *in situ* gelling ophthalmic drug delivery systems. However, the amount of PAA required to form stiff gel upon instillation in the eye is not easily neutralized by the buffering action of tear fluid. Combination PAA with a suitable viscosity enhancing polymer e.g. HPMC or MC allows a reduction in the PAA concentration without comprising the *in situ* gelling properties. The formulation containing Carbopol®940 and Methocel E50LV (HPMC) afforded sustained release of ofloxacin over an 8-h period.

C. Rectal Delivery

The rectal route may be used to deliver many types of drugs those are formulated as liquid, semi-solid (ointments, creams and foams) and solid dosage forms (suppositories). Conventional suppositories often cause discomfort during insertion. In addition, suppositories are unable to be sufficiently retained at a specific position in the rectum, sometimes they can migrate upwards to the colon, that makes them possible for drug to undergo the first-pass effect.

Novel *in situ* gelling liquid suppositories with gelation temperature at 30–36°C were developed using poloxamer 407 and/or poloxamer 188 to confer the temperature-sensitive gelation property. It is also possible to develop a vehicle for short chain fatty acid enemas using 18% poloxamer 407 solution. After gelation at 37°C, it allows control release of short chain fatty acids. Thermoreversible xyloglucan gels are useful for rectal drug delivery.

D. Vaginal Delivery

Formulations based on a thermoplastic graft copolymer that undergo *in situ* gelation have been developed to provide prolonged release of active ingredients such as nonoxynol-9, progestins, estrogens, peptides and proteins.
A mucoadhesive thermosensitive gel containing combination of poloxamers and

polycarbophil exhibited increased and prolonged antifungal activity of clotrimazole in comparison with conventional PEG-based formulation.

E. Peroral Delivery

The pH-sensitive hydrogels have a potential use in site-specific delivery of drugs to specific regions of Stimuli-sensitive hydrogels in controlled and sustained drug delivery the GI tract. Hydrogels made of varying proportions of PAA derivatives and cross-linked PEG allowed preparing silicone microspheres, which released prednisolone in the gastric medium and showed gastroprotective property. Cross-linked dextran hydrogels with a faster swelling under high pH conditions, likewise other polysaccharides such as amidaded pectins, guar gum and inulin were investigated in order to develop a potential colon-specific drug delivery system.

The formulations of gellan gum and sodium alginate both containing complexed calcium ions undergo gelation by releasing of these ions in the acidic environment of the stomach. Such formulations were developed for oral delivery of paracetamol.

F. DERMAL AND TRANSDERMAL DELIVERY

Thermally reversible gel of Pluronic F127 was evaluated as vehicle for the percutaneous administration of indomethacin. [73] In-vivo studies suggest that 20% w/w aqueous gel may be of practical use as a base for topical administration of the drug. Poloxamer 407 gel was found suitable for transdermal delivery of insulin. [74] The combination of chemical enhancers and iontophoresis resulted in synergistic enhancement of insulin permeation.

G. NASAL DELIVERY

Nasal formulations of AEA with chlorpheniramine maleate and tetrahydrozoline hydrochloride were investigated. [75] The findings suggest that

liquid AEA formulations facilitate the instillation into the nose and the hydrogel formed on the mucous membrane provide controlled drug release.

In the nutshell, drug delivery has undergone a revolutionary advancement in the past few years. With the advent of novel delivery systems, various drug molecules have been revived of their therapeutic and commercial benefits. The introduction of stimuli-responsive systems has further strengthened the link between therapeutic need and drug delivery. A lot of research is ongoing in various laboratories to explore stimuli-responsive hydrogels as drug delivery systems for better patient care. The success of hydrogels as delivery systems can be judged by several marketed preparations. In the present scenario, the major considerations during the formulation of hydrogel-based drug products are their mechanical strength and response-time in a physiological environment. Fast-responding hydrogels releasing maximal drug in less time while maintaining the structural integrity in a biological system will be the more appreciated delivery systems. Moreover, a high level of *in vitro–in vivo* correlation in their performance will determine their future success. The exploitation of these polymeric networks for improved therapeutic efficacy will open newer arenas in drug delivery.

PREVIOUS QUESTIONS

Bioadhesive systems

1. Which are potential sites and dosage forms for bioadhesion? Draw a general schematic diagram for BDDS and classify them. Write a note on ex-vivo and in-vivo methods to study this system.
2. Discuss about theories related to Bioadhesion.
3. Discuss evaluation of bioadhesive drug delivery system.
4. Classify various factors affecting bioadhesion/mucoadhesion under separate/distinct heads and discuss in detail two factors from each head.
5. Define and explain bioadhesion, explain the theories of Bioadhesion and enumerate the properties of an ideal polymer for mucoadhesive drug delivery system

Insitu gels

1. What is in-situ gel? Classify them and suggest its applications.
2. Discuss various approaches of in-situ gelation.
3. Note on: Insitu gels