Natural and synthetic polymers used in Bioadhesive delivery system

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Abstract: *Various biopolymers show the bioadhesive properties and have been utilized for various therapeutic purposes in medicine. 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 in the development of products for various biomedical applications and surgical glue. The bioadhesive polymers can be broadly classified into two groups, namely specific and nonspecific. The specific bioadhesive polymers (e.g. lectins, fibrin) 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 is for the development of pharmaceutical formulations. Various other polymers which have Mucoadhesive property are HPMC, PEG, tragacanth, sodium alginate, guar gum, MC, CMC, sodium CMC etc. 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 by-products, inhibit the enzymes present at the delivery site and enhance the penetration of the active agent. Current use of mucoadhesive polymers to increase contact time for a wide variety of drugs and routes of administration has shown dramatic improvement in both specific therapies and more general patient compliance. Hence mucoadhesive polymers can be used as means of improving drug delivery through different routes like gastrointestinal, nasal, ocular, buccal, vaginal and rectal.*

Key Words: *bioadheive, mucoadhesive, synthetic polymers, natural polymers*

1. INTRODUCTION:

The word ‘polymer’ is derived from Greek words, poly which means ‘many’ and meros means ‘parts or units of high molecular mass’. Each molecule consists of a very large number of single structural units joined together in a regular manner by covalent bonds. Polymers are the giant molecules of high molecular weight called macromolecules which are formed by linking together a large number of small molecules, called monomers. The process by which monomers combine to form polymer is known as polymerization. The polymerization is defined as a chemical reaction in which two or more substances combine together with or without evolution of water, heat or any other solvents to form a molecule of high molecular weight. The product obtained is called polymer and the starting material from which the polymers are made is called monomer. The polymeric delivery system is mainly intended to achieve either a temporal or spatial control of drug delivery. The introduction of the first synthetic polymer-based drug delivery system led to a heightened interest in the design and synthesis of novel biodegradable polymers that obviated the need to remove the drug delivery system, the non-biodegradable polymeric system. Recognizing that intimate contact between a delivery system and an epithelial cell layer will improve the residence time as well as the efficiency of the drug delivery system resulted in the design of bioadhesive polymers. Further advancements in polymer science led to ‘smart’ polymeric hydrogel systems that can self-regulate the delivery of a bioactive agent in response to a specific stimulus. 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 for a 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 a 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 non-specific. The specific bioadhesive polymers (e.g., lectins, fimbrin) have the ability to adhere to specific chemical structures within the biological molecules while the non-specific bioadhesive polymers (e.g., poly(acrylic 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 a polyethylene sheet was laminated with a blend of sodium carboxymethylcellulose and polyisobutylene 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, sodiumcarboxymethylcellulose, guargum, hydroxyethylcellulose, karya gum, methylcellulose ,poly(ethyleneglycol) (PEG)mucoadhesiveproperties .During the 1980s poly(acrylicacid), hydroxypropylcellulose and sodium carboxymethylcellulose were widely explored for the development of formulations having mucoadhesive properties.

In biological systems, four types of bioadhesion can be distinguished.

- Adhesion of a normal cell to another normal cell.
- Adhesion of a cell with a foreign substance.
- Adhesion of a normal cell to a pathological cell
- Adhesion of an adhesive to a biological substrate.

Bioadhesions are classified into three types based on phenomenological observation, rather than on the mechanisms of bioadhesion:

Type I: Bioadhesion is characterized by adhesion occurring between biological objects without involvement of artificial material. e.g., cell fusion and cell aggregation.
Type II: Bioadhesion can be represented by cell adhesion onto culture dishes or adhesion to a variety of substances including metals, woods, and other synthetic materials
Type III: Bioadhesion can be described as adhesion of artificial substances to biological substrates such as adhesion of polymers to skin or other soft tissues.

A term 'Bioadhesive' is defined as a substance that is capable of interacting with biological materials and being retained on them or holding them together for extended period of time. For drug delivery purposes, the term bioadhesion implies attachment of a drug carrier system to a specified biological location. The biological surface can either be an epithelial tissue or it can be the mucous coat on the surface of a tissue. If adhesive attachment is to a mucous coat, the phenomenon is referred to as 'Mucoadhesion'. Leung and Robinson described mucoadhesion as the interaction between a mucin and a synthetic or natural polymer.

Table:1

Representative list of polymers used in drug delivery.

Classification	**Polymer**
Natural polymers	Protein-based polymers Collagen, albumin, gelatin Polysaccharides Agarose, alginate, carrageenan, hyaluronic acid, dextran, chitosan, cyclodextrins
Synthetic polymers	Biodegradable Polyesters Poly(lactic acid), poly(glycolic acid), poly(hydroxy butyrate), poly(εcaprolactone), poly(β-malic acid), poly(dioxanones) Polyanhydrides Poly(sebacic acid), poly(adipic acid), poly(terphthalic acid) and
various copolymers	Polyamides Poly(imino carbonates), polyamino acids Phosphorous-based polymers Polyphosphates, polyphosphonates, polyphosphazenes Others Poly(cyano acrylates), polyurethanes, polyortho esters, polydihydropyrans, polyacetals
Non-biodegradable	**Cellulose derivatives** Carboxymethyl cellulose, ethyl cellulose, cellulose acetate, cellulose acetate propionate, hydroxypropyl methyl cellulose Silicones Polydimethylsiloxane, colloidal silica Acrylic polymers Polymethacrylates, poly(methyl methacrylate), poly hydro(ethyl- methacrylate) Others Polyvinyl pyrrolidone, ethyl vinyl acetate, poloxamers, poloxamines

TABLE:2 **Factors influencing biodegradation of polymers.**
Chemical structure and composition Physico-chemical factors (ion exchange, ionic strength, pH) Physical factors (shape, size, chain defects) Morphology (amorphous, semicrystalline, crystalline, microstructure, residual stress) Mechanism of degradation (enzymatic, hydrolysis, microbial) Molecular-weight distribution Processing conditions and sterilization process Annealing and storage history Route of administration and site of action

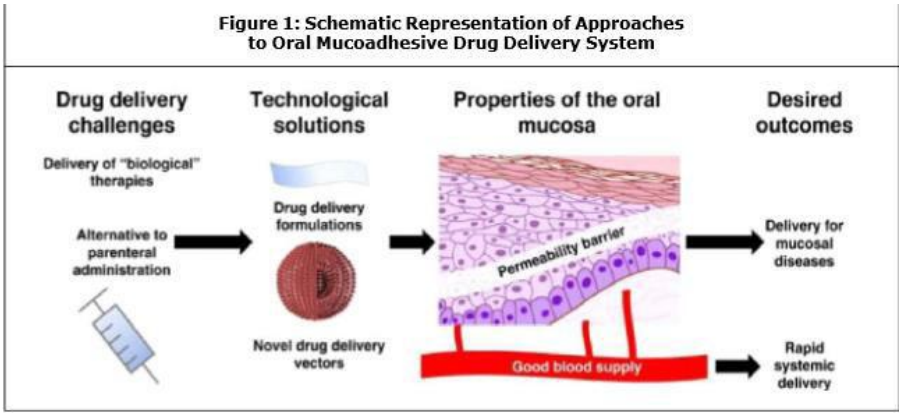
2. SIGNIFICANCE OF BIOADHESION:

The idea of mucoadhesive was derived from the need to localize drugs at a certain site in the body. Increasing the residence time of the drug at the absorption site can enhance extent of drug absorption, for example in ocular drug delivery; less than two minutes are available for drug absorption after installation of drug solution into the eye, since it is removed rapidly through solution Asian drainage, the ability to extend contact time of an ocular drug delivery system would undoubtedly improve bioavailability of drugs. Since many drugs are absorbed only from the upper small intestine, localizing oral drug delivery systems in the stomach or in the duodenum would significantly improve the extent of drug absorption. Also they provide intimate contact between dosage form and the absorbing tissue, which may result in high drug concentration in a local area and hence high drug flux through the absorbing tissue. Furthermore, the intimate contact may increase the total permeability of high molecular weight drugs such as peptides and proteins. Absorption through nasal mucus is similar to the i.v. infusion, moreover buccal mucus permits the systemic entry of drugs with high first pass metabolism in stomach and a polymer used also controls drug electrical double layer at the interface. Adhesion occurs due to attractive forces across the double layer.

3. THEORY OF MUCOADHESIVE SYSTEM:

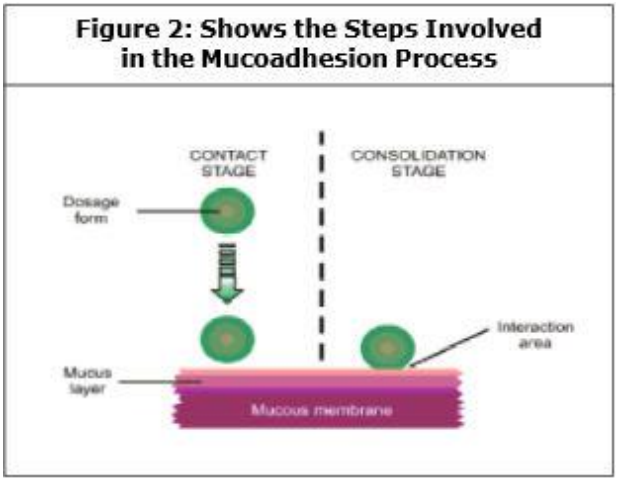
Adsorption Theory:

Figure 1: Schematic Representation of Approaches to Oral Mucoadhesive Drug Delivery System



According to the adsorption theory, after an initial contact between two surfaces, the material adheres because of surface forces acting between the atoms on the two surfaces. Two types of chemical bonds resulting from these forces can be distinguished,Primary chemical bonds of covalent nature, which are undesirable in bioadhesion because of their high strength, which may result in permanent bonds.Secondary chemical bonds having many different forces of attraction,

Figure 2: Shows the Steps Involved in the Mucoadhesion Process



Wetting theory: is predominantly applicable to liquid bioadhesive systems. It analyzes adhesive and contact behavior in terms of the ability of a liquid or paste to spread over a biological system. The work of adhesion (Wa) is defined as the energy per square centimeter released when $A = \pi r^2$an interface is formed and is expressed in terms of surface and interfacial tension Y. The work of adhesion is given by, $Wa = YA + YB - YAB$ Where A and B refer to the biological membrane and the bioadhesive formulation respectively. The work of cohesion is given by, $Wc = 2YA$ or $2YB$

For a bioadhesive material B spreading on a biological substrate A, the spreading coefficient is given by, $SB/A = YA - YB + YAB\ SB/A$ should be positive for a bioadhesive material to adhere to a biological membrane.

Diffusion Theory:

According to diffusion theory, the polymer chains and the mucus mix to a sufficient depth to create a semi-permanent adhesive bond .The exact depth to which the polymer chain penetrates the mucus depends on the diffusion coefficient and the time of contact. Fracture Theory attempts to relate the difficulty of separation of two surfaces after adhesion.

Fracture theory equivalent to adhesion strength is given by, $G = (E\ \Delta\ /L)\ 1/2$ Where E is Young's modulus of elasticity, Δ is fracture energy and L is critical crack length when two surfaces are separated. Water molecules adjacent to non-polar groups form hydrogen bonded structures, which lowers the system entropy. There is therefore an increase in the tendency of non-polar groups to associate with each other to minimize this effect. For bioadhesion to occur, a succession of following phenomena is required. The first stage involves an intimate contact between a bioadhesive and a membrane, either from a good wetting of the bioadhesive surface or from the swelling of the bioadhesive. In second stage, once contact is established, penetrations of the bioadhesive into the crevice of tissue surface or interpenetration of the chains of the bioadhesive with that of the mucus take place. On a molecular level, mucoadhesion can be explained on the basis of molecular interactions. The interaction between two molecules is composed of attraction and repulsion. Attractive interactions arise from van der Waals forces, electrostatic attraction, hydrogen bonding, and hydrophobic interaction. Repulsive interactions occur because of electrostatic and steric repulsion. For mucoadhesion to occur, the attractive interaction should be larger than nonspecific repulsion. Several theories have been proposed to explain the fundamental mechanisms of adhesion.

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

Bioadhesive polymers: Polymers that can adhere to either hard or soft tissue are employed for the purpose of bioadhesion. These are generally the polymers with numbers hydrophilic function groups that can form hydrogen bonds, e.g., carboxyl, hydroxyl, amide and sulfate groups. In the presence of water, hydrogen bonding appears to play a significant role in mucoadhesive. Some mucoadhesive polymers can hydrate in an aqueous media to form a gel.

The mucoadhesive used in oral drug delivery should meet the following requirments:

- Adhesiveness with the mucus layer, to provide adequate contact.
- Ability to swell and allow drug release
- Ability to prolong the residence time of the drug at the site of administration.
- Lack of interaction with the mucosal surface, to avoid cytotoxicity or other irreversible alterations of the mucosal surface.
- Biocompatibility with the mucosal surface, to avoid cytotoxicity or other irreversible alterations of the mucosal surface.
- Biodegradability, to allow the physical clearance of the mucosal surface.
- Remain unaffected by hydrodynamic conditions, food and Ph.

4. CHARACTRISTICS OF BIOADHESIVE POLYMERS:

Hydrophilic polymers: are water soluble polymers that swell when in contact with water and eventually undergo complete dissolution. These polymers show high bioadhesiveness to the mucosa in the dry state, but the bioadhesive nature deteriorates as they start dissolving.

Hydrogels cross linked polymers: swell when they come in contact with water. The extent of swelling depends on the degree of cross linking.

When mobile at the wet mucosal surface they orientate various carboxylic groups present in them towards mucosa and interpenetrate deeper into the mucosa.

Thermoplastic polymers: are hydrophobic polymers and include both bioerodible polymers. Absorption studies have shown that mucin has strong affinity for hydrophobic surfaces. Additionally, these polymers are nontoxic and non-irritant.

4.1. Polymer-Related Factors

(a) Molecular Weight

The bioadhesion property depends on the molecular weight of selected bioadhesive polymer. Bioadhesion is successful if molecular weight is 100,000 and more.

Example: Polyethylene glycol (PEG) with a molecular weight of 20,000 has little adhesive character, whereas PEG with 200,000 molecular weight has improved, and a PEG with 400,000 has superior adhesive properties. The bioadhesive nature improves with increasing molecular weight for linear polymers.

Adhesiveness of a nonlinear structure follows different trend.

Example: The adhesive strength of dextran, with a very high molecular weight of 19,500,000 is similar to that of PEG, with a molecular weight of 200,000. The reason for this similarity may be that the helical conformation of dextran may shield many of the adhesive groups, which are primarily responsible for adhesion, unlike the conformation of PEG.

(b) Concentration of active polymers

If there is an optimum concentration of bioadhesive polymer, produce maximum bioadhesion. In highly concentrated systems, beyond the optimum level the adhesive strength drops significantly because the coiled molecules become separated from the medium so that the chains available for interpenetration become limited.

(c) Flexibility of polymer chains

If the polymer chains decrease, the effective length of the chain that can penetrate into mucous layer decreases, which reduces bioadhesive strength. It is critical for interpenetration and entanglement.

(d) Spatial conformation

Besides molecular weight or chain length, spatial conformation of a molecule is also important. Example: High molecular weight of 19,500,000 for dextrans, they have similar adhesive strength to the polyethylene glycol with a molecular weight of 200,000. The helical conformation of dextran may shield many adhesively active groups, primarily responsible for adhesion, unlike PEG polymers which have a linear conformation.

4.2. Environment Related Factors

(a) Applied strength

To place a solid bioadhesive system, it is necessary to apply a defined strength. Whatever the polymer, poly acrylic acid / vinyl benzene or carbopol 934, the adhesion strength increases with the applied strength or with the duration of its application. If high pressure is applied for a sufficiently long period of time, polymers become mucoadhesive even though they do not have attractive interaction with mucin.

(b) pH

Bioadhesion can be influenced by the charges present on the surface of mucus as well as certain ionisable bioadhesive polymers. Mucus will have a different charge density depending on pH due to difference in dissociation of functional groups on the carbohydrate moiety and the amino acids of the polypeptide backbone. pH of the medium is important for the degree of hydration.

Example: Poly acrylic acid, showing consistently increased hydration from pH 4 to 7 and then decrease as alkalinity and ionic strength increases.

(c) Initial Contact Time

Contact time between the bioadhesive and mucus layer determines the extent of swelling and interpenetration of the bioadhesive polymer chains. Moreover, bioadhesive strength increases as the initial contact time increases.

(d) Swelling

It depends on the polymer concentration, ionic concentration, as well as the presence of water. Over hydration results in the formation of a slippery mucilage without adhesion.

1) Natural polymers

A) Protein based polymers: collagen, albumin, gelatin

B) Polysaccharides: Alginates, Cyclodextrines, Chitosan, Dextran, Agarose, Hyaluronic acid, Starch, Cellulose

2) Synthetic polymers

I) Biodegradable polymers

A) Polyesters: Polylactic acid, Polyglycolic acid, Polyhydroxyl butyrate, Polycaprolactone, Poly Doxanones

B) Polyanhydride: Polyadipic acid, Polyterphthalicacid, Polysebacic acid and Various copolymers

C) Polyamides: Poly iminocarbonates, Poly amino acids.

D) Phosphorous Based polymers: Polyphosphates, Polyphosphonates, Polyphosphazenes.
E) Others: Poly cyanocrylates, Poly urethanes, Poly ortho esters, Polyacetals.
II) Non biodegradable polymers
A) Cellulose derivatives: Carboxymethylcellulose, Ethyl cellulose, Cellulose acetate HPMC.
B) Silicones: Polydimethyl siloxanes, Collodial silica, Polymethacrylates
C) Others: PVP, EVA, Poloxamines.

Natural polymers:-
Collagen: Collagen is a major natural protein component. It is a triple helix molecular structure. Nineteen types of collagen molecules have been isolated, characterized, and reported in both medical and pharmaceutical applications. Collagen has been widely used in pharmaceutical applications in drug delivery system because of its good biocompatibility, low antigenicity, and degradability upon implantation. Collagen gels are one of the first natural polymers used for drug delivery and tissue engineering.

Gelatin: Gelatin is a common natural polymer (water soluble polymer) or protein which is normally produced by denaturing collagen. It has been used in pharmaceutical and medical applications due to its outstanding properties such as biodegradability, biocompatibility, and low antigenicity. It is one of the natural polymers used as support material for gene delivery, cell culture, and more recently tissue engineering. Gelatin based systems have the ability to control release of bioactive agents such as drugs, protein, and dual growth factors. It is possible to incorporate liposome-loaded bioactive compounds into PEG-gelatin gel.

Albumin: Serum albumin was conjugated to poly-(ethylene glycol) (PEG) and cross-linked to form mono-PEGlycolated albumin hydrogels. These hydrogels were used as a basis for drug carrying tissue engineering scaffold materials.

Alginate: It is an example of a naturally occurring linear polysaccharide. It is extracted from seaweed, algae, and bacteria. The fundamental chemical structure of alginate is composed of (1–4)-b-D-mannuronic acid (M) and (1–4)-a-L-guluronic acid (G) units in the form of homo polymeric (MM- or GG-blocks) and hetero polymeric sequences (MG or GM-blocks). Alginate and their derivates are widely used by many pharmaceutical scientists for drug delivery and tissue engineering applications due to its many properties such as biocompatibility, biodegradability, low toxicity, non-immunogenicity, water solubility, relatively low cost, gelling ability, stabilizing properties, and high viscosity in aqueous solutions.

Dextran: Dextran is a natural linear polymer of glucose linked by a 1–6 linked-glucoyranoside, and some branching of 1,3 linked sidechains. Dextran is synthesized from sucrose by certain lacticacid bacteria, the best-known being Leuconostoc mesenteroides and Streptococcus mutans. There are two commercial preparations available, namely dextran 40 kilodaltons (kDa) and dextran 70 Kilo daltons (kDa).
In pharmaceutics, dextran has been used as model of drug delivery due to its characteristics such as water solubility, biocompatibility, and biodegradability. Dextran is a potential polysaccharide polymer that can sustain the delivery of proteins, vaccines, and drugs.

Chitosan: Chitosan is a natural poly cationic copolymer consisting of glucosamine and N-acetyl glucosamine units. It is mostly obtained by deacetylation of chitin derived from the exoskeleton of crustaceans. Chitosan has valuable properties as biomaterials because it is considered to be biocompatible, biodegradable property. The cationic character and the potential functional group make it an attractive biopolymer for many biomedical and pharmaceutical applications. As a pharmaceutical excipient, chitosan has been used in many formulations like powders, tablets, emulsions and gels. Chitosan shows mucoadhesive properties and antimicrobial properties. Chitosan can also be mixed with nonionic surfactant such as sorbitan ester to make emulsion like solutions or creams. This polymer possesses OH and NH2 group that can give rise to hydrogen bonding. These properties are considered essential for mucoadhesion.

Uses: Masking of bitter taste, as a drug carrier, as a tablet excipient, delivery platform for parenteral formulations, disintegrant and tablet coating.

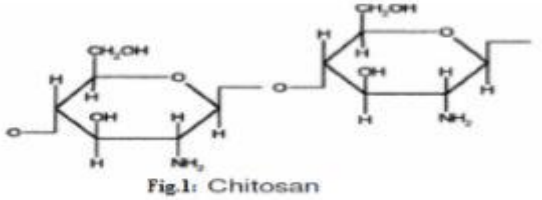


Fig.1: Chitosan

Cellulose Derivatives : Cellulose is the most abundant naturally occurring biopolymer. Various natural fibers such as cotton and higher plants have cellulose as their main constituent. It consists of long chains of anhydro-D-glucopyranose units (AGU) with each cellulose molecule having three hydroxyl groups per AGU, with the exception of the terminal ends. Cellulose is insoluble in water and most common solvents, the poor solubility is attributed primarily to the strong intramolecular and intermolecular hydrogen bonding between the individual chains. In spite of its poor solubility characteristics, cellulose is used in a wide range of applications including composites, netting, upholstery, coatings, packing, paper, etc.
Examples: carboxymethyl cellulose (CMC), methyl cellulose (MC), hydroxyethylcellulose (HEC), hydroxypropyl methyl cellulose (HPMC), hydroxylpropyl cellulose(HFC), ethyl hydroxyethyl cellulose (EHEC), and methyl hydroxyethyl cellulose(MHEC).

Starch: Plants synthesize and stored starch in their structure as an energy reserve. It is generally deposited in the form of small granules or cells with diameters between 1-100 μm. After cellulose, starch is the most abundant carbohydrate available from plant kingdom as raw material. The estimated world production of starch amounts to 58 million tonnes, extracted from maize (46 million), wheat (4.6 million), potatoes (3.5 million), and the remainder coming from rice and cassava roots (tapioca). Starch is the main carbohydrate in plants and acts as a reserve food supply for periods of growth, dormancy and germination. The properties of each starch are strongly dependent on their plant source. Starch is a heterogeneous polymer of α-D-glucose units. The anhydrous glucose units (AGUs) are mainly linked by α-(1, 4)-bonds and to some extent by α-(1 , 6)-linkages. The biopolymer consists of two distinguished structural forms: amylose and amylopectin.

Amylose is mainly found as a long linear polymer containing about several hundred α-(1, 4)-linked glucose units (up to 6000 AGUs), with a molecular weight of 105-106 g mol-1. In the solid state, the chains very easily form single or double helices.

In contrast, amylopectin is a highly branched molecule with a molecular weight of 107-109 gmol-1. The branched polymer contains α-(1,4)-linked glucose units but has additional α-(1,6)glucosidic branching points which are believed to occur every 10 to 60 glucose units, i.e. 5% of the glucose moieties are branched.

Advantages: Ease of tablet preparation, the potential of a constant release rate (zero-order) for an extended period of time and its ability to incorporate high percentages of drugs with different physicochemical properties.

Hyaluronic acid: Hyaluronic acid also called as Hyaluronan and Hyaluronate (HA) and it is a biodegradable, biocompatible, and viscoelastic linear polysaccharide of molecular weight range (1000 to 10,000,000 Da). It is a naturally occurring biopolymer,Naturally occurring hyaluronic acid may be found in the tissue of higher animals. It is found in greatest concentrations in the vitreous humor of the eye and in the synovial fluid of articular joints. Hyaluronic acid comprises linear, unbranching, polyanionic disaccharide units consisting of glucuronic acid (GlcUA) an N-acetyl glucosamine (GlcNAc) joined alternately by β-1-3 and β-1-4 glycosidic bonds. The viscoelastic property of hyaluronic acid solutions that is important in its use as a biomaterial is controlled by the concentration and molecular weight of the hyaluronic acid chains [87]. Cyclodextrin:- They are cyclic oligosaccharides consisting of six to eight glucose units joined through α-1, 4 glucosidic bonds. Cyclodextrins remains intact during their passage throughout the stomach and small intestine of the GI tract. In colon, they undergo fermentation in the presence of vast colonic microfloras into small monosaccharide and thus absorbed from these regions. β-cyclodextrins are degraded to a very small extent in the small intestine but are completely digested in the large intestine.

Biodegradable polymer: Biodegradation is a natural process by which organic chemicals in the environment are converted to simpler compounds, mineralized and redistributed through elemental cycles such as carbon, nitrogen and sulphur cycles. Biodegradable polymers have been widely used in biomedical applications because of their known biocompatibility and biodegradability. Biodegradable polymers are intended for temporary aids, such as sutures, tissue-supporting scaffolds, and drug delivery devices. Biodegradable polymers are suitable for drug delivery applications and biomedical applications.

Advantage: Biodegradable polymers are broken down into biologically acceptable molecules that are metabolized and removed from the body via normal metabolic pathways.

Synthetic Polymers:

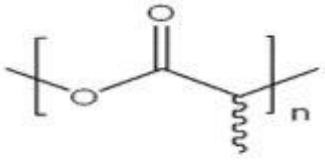


Fig. 2: General structure of PLA

Polyester: Poly lactic acid (PLA):- PLA is thermoplastic biodegradable polymer produced synthetically by polymerization of lactic acid monomers. Lactic acid is produced by fermentation of natural carbohydrates for example, maize or wheat or waste products from the agricultural or food industry. PLA is degraded by hydrolysis (the breaking of a chemical bond by adding water to it) of the backbone esters of the polymer. The esters are broken at random, so that the PLA chains in the material get shorter and shorter until monomers of lactic acid start to come loose and the plastic essentially dissolves. This process is called bulk degradation.
Uses: Producing compost bags and disposable tableware, biomedical applications such as sutures, stents, dialysis media and drug delivery devices.

Polyglycolic acid (PGA): PGA is commonly obtained by ringopening polymerization of the cyclic diester of glycolic acid, glycolide. PGA is a hard, tough, crystalline polymer with a melting temperature of 225 °C and a glass transition temperature (Tg) of 36 °C. Polyesters such as PLA, PGA is insoluble in most common polymer solvents. PGA has excellent fiber-forming properties and was commercially introduced in 1970 as the first synthetic absorbable suture under the trade name Dexon. The low solubility and high melting point of PGA limits its use for drug delivery applications, since it cannot be made into films, rods, capsules, or microspheres using solvent or melt techniques.

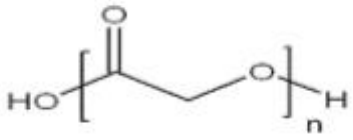


Fig. 3: General structure of PGA

Polyhydroxybutyrate (PHB): PHB is a biopolymer, which is present in all living organisms. Many bacteria produce PHB in large quantities as storage material. It is not toxic and is totally biodegradable. PHB and its copolymers have attracted much attention because they are produced biosynthetically from renewable resources. Microcapsules from PHB has been prepared by various techniques and investigated for the release of bovine serum albumin. PHB has also been suggested as a suitable matrix for drug delivery in veterinary medicine.

Poly (lactide-co-glycolide), PLGA: Among the co-polyesters investigated, extensive research has been performed in developing a full range of PLGA polymers. Both L- and DL-lactides have been used for co-polymerization. The ratio of glycolide to lactide at different compositions allows control of the degree of crystallinity of the polymers. When the crystalline PGA is co-polymerized with PLA, the degree of crystallinity is reduced and as a result this leads to increases in rates of hydration and hydrolysis. Higher the content of glycolide, the quicker the rate of degradation.PLGA is used in drug delivery applications. Non-steroidal anti-inflammatory drugs, e.g., diflunisal and diclofenac sodium have been incorporated into PLGA microspheres and investigated for the treatment of rheumatoid arthritis, osteoarthritis, and related diseases.

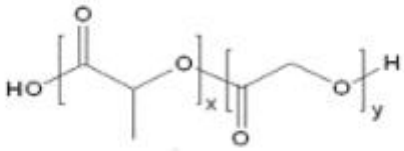


Fig. 4: General structure of PLGA

Poly (e-caprolactone),PCL:PCL is obtained by ring-opening polymerization of the 6-membered lactone,e-caprolactone (e-CL). PCL has a melting temperature of 61 °C. It is tough and flexible. Thus, PCL is in the rubbery state and exhibits high permeability to low molecular species at body temperature. These properties, along with its biocompatibility, make PCL a promising candidate for controlled release applications.

Polydioxanone (PDS): PDS is made by a ring-opening polymerization of the p-dioxanone monomer. It is characterized by a glass transition temperature in the range of –10 to 0°C and a degree of crystallinity of about 55%. Materials prepared with PDS show enhanced flexibility due to the presence of an ether oxygen within the backbone of the polymer chain, when used in vivo, it degrades into monomers with low toxicity.

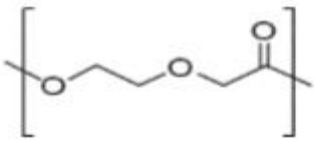


Fig. 5: General structure of PD

Polyanhydrides: Polyanhydride are class of biodegradable polymer characterized by anhydride bonds that connect repeat unit of polymers backbone chain. Poly (anhydride-esters) are polymeric compounds consisting of salicylic acid moieties bridged by linker structures.

Polyamide: The synthetic aliphatic polyamides are polymeric compounds frequently referred to as Nylons which form an important group of poly condensation polymers. They are linear molecules (i.e. aliphatic) that are semi-crystalline and thermoplastic in nature. Polyamide chain consists of amide groups separated by alkane segments and the number of carbon atoms separating the nitrogen atoms which defines the particular polyamide type. The aliphatic polyamides are very useful and versatile material. The physical properties as well as the extensive clinical use of the synthetic aliphatic polyamides as surgical sutures demonstrates their biocompatibility and non-toxicity and make them attractive for use in the design and development of drug delivery systems.

Phosphorous based derivatives:
Polyphosphazenes: It consists of phosphorous atoms attached to either carbon or oxygen.
Use: Delivery of proteins.

Others:
Polyorthoesters: POE are another family of polymers identified as biodegradable polymers suitable for orthopaedic applications. The degradation of the lactide segments produces carboxylic acids, which catalyze the degradation of the orthoester. POE increase bone growth in comparison with poly (dilactide-co-glycolide).

5. NEW GENERATION OF MUCOADHESIVE POLYMERS:

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 subdomains present in mucin which can substantially improve the mucoadhesive properties of the polymers.

Examples:chitosaniminothiolane,poly(acrylicacid)cysteine,poly(acrylicacid)–homocysteine,chitosan–thioglycolicacid,chitosan–thioethylamidine,alginate–cysteine, poly(methacrylic acid)–cysteine and sodium carboxymethylcellulose–cysteine.

Polyox WSR: A class of high molecular weight polyethylene molecular weight polyethylene oxide homopolymers having the following properties, a. Water soluble hydrophillic nature b. High molecular weight c. Functional group for hydrogen bonding d. Biocompatible and nontoxic e. Can be formulated into tablets, films, gels, microcapsules, syrups

6. EVALUATION OF MUCOADHESIVE DRUG DELIVERY SYSTEMS:

Measuring the force of attachment: The adhesive strength at bonding interface can be measured by measuring the force required to detach one entity from the other through the application of an external force. Hence the destruction of adhesive bond is usually under the application of either a shearing, tensile or peeling force.

Fluorescent probe method: In this method the membrane lipid bilayered and membrane proteins were labeled with pyrene and fluorescein isothiocyanate, respectively. The cells were mixed with the mucoadhesive agents and changes in fluorescence spectra were monitored. This gave a direct indication of polymer binding and its influence on polymer adhesion.

Thumb test: The adhesiveness is measured by the difficulty of pulling the thumb from the adhesive as a function of the pressure and the contact time. Although the thumb test may not be conclusive, it provides useful information on peel strength of the polymer.

In vitro residence time study: The mucoadhesive properties of tablets were evaluated by in vivo residence time. A 1-cm by 1-cm piece of porcine buccal mucosa was tied onto a glass slide (3-inch by 1-inch) using thread. Tablet was stuck onto the wet, rinsed, tissue specimen, by applying light force with a fingertip for 30 seconds. The prepared slide was hung onto one of the groves of a USP tablet disintegrating test apparatus. The disintegrating test apparatus was operated such that the tissue specimen was given regular up and down movements in a beaker containing the dissolution medium (0.01 N HCl). At the end of 3 hour, the detachment of tablet from tissue was checked and the time of detachment was recorded as the in vivo residence time.

GI transit study using radio-opaque markers: It is a simple procedure involving the use of radio-opaque markers, e.g. barium sulfate, encapsulated in bioadhesive to determine the effects of bioadhesive polymers on GI transit time.

Faeces collection (using an automated faeces collection machine) and X-ray inspection provide a non-invasive method of monitoring total GI residence time without affecting normal GI motility.

CONCLUSION:

Mucoadhesive polymers may provide an important tool to improve the bioavailability of the active agent by improving the residence time at the delivery site. The various sites where mucoadhesive polymers have played an important role include buccal cavity, soft palate, gingival, nasal cavity, rectal lumen, vaginal lumen and gastrointestinal tract. Development of novel mucoadhesive delivery systems are being undertaken so as to understand the various mechanism of mucoadhesion and improved permeation of active agents.Advantages such as mucoadhesion, an increase in the residence time of the polymer, penetration enhancement, and enzymatic inhibition. This class of polymers has enormous potential for the delivery of therapeutic macromolecules, genes, and vaccines. Mucoadhesive dosage forms have a high potential of being useful means of delivering drugs to the body. Current use of mucoadhesive polymers to increase contact time for a wide variety of drugs and routes of administration has shown dramatic improvement in both specific therapies and more general patient compliance. Hence mucoadhesive polymers can be used as means of improving drug delivery through different routes like gastrointestinal, nasal, ocular, buccal, vaginal and rectal. Many potential mucoadhesive systems are being investigated which may find their way into the market in near future. Drug delivery through the numerous gastroretentive approaches has opened a new horizon for effective way of increasing patient compliance and increasing bioavailability of variety of drugs through oral rout. Many approaches with use of different polymers and other constituents can produce different range of gastroretentive systems. Especially the floating drug delivery system is the most widely used in gastroretentive dosage forms. However a lot of work is still needed to be done to overcome the different physiological and pharmaceutical barriers to develop the more effective gastroretentive dosage forms.

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