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Research Article

POLYMERS IN MUCOADHESIVE DRUG DELIVERY SYSTEM-LATEST UPDATES

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ABSTRACT

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.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, 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,guargum, MC, CMC, sodiumCMC 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 byproducts, 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.

Keywords: Bioadhesion, Mucoadhesion, Mucoadhesive polymers, Evaluation, factors mucoadhesion theories

INTRODUCTION

Mucoadhesion process involves in the polymeric drug delivery system which is a complex process by the processes such as wetting, adsorption, chemial bonding etc. Mucoadhesion process is mainly influenced by polymeric based properties like degree of cross linking, chain length, and various functional groups in polymer structure. Mucoadhesive systems have widely used throughout many mucosal covered organelles for active ingredients delivery for local or systemic effect[1].

The concept of mucoadhesion was introduced in the field of controlled release drug delivery systems in the early 1980s [1-2]. For drug delivery purpose, the term bioadhesion implies attachment of a drug carrier system to a specific biological location.

If adhesive attachment is to a mucous, the phenomenon is referred to as mucoadhesion. Mucoadhesion is relatively new concept in drug delivery system. Mucoadhesion delivers the drug by adhering to the mucus membrane. Various mucosal routes for drug delivery are

- Buccal /oral route
- Nasal route
- Ocular route
- Vaginal route
- Gastrointestinal route

Need of mucoadhesive delivery

Oral administration is the major route for drug delivery. Oral controlled release systems are used for controlled action of active ingredients to the targeted site. But oral controlled release systems have many problems such as first pass hepatic metabolism, enzyme degradation, swallowing problem etc. So, as compared to oral controlled release systems, mucoadhesive delivery system have several advantages like prolongation of residence time, drug targeting, intimate contact between dosage form and the absorptive mucosa. In addition, mucoadhesive dosage forms have been used to target local disorders at the mucosal surface to reduce dose and to minimize the side effects. Mucoadhesive formulations use polymers as the adhesive component. These polymers are water soluble. When polymers are used in a dry form, they attract water from the mucosal surface and leads to a strong interaction which increases the retention time over the mucosal surfaces. Prolonged contact time of a drug with a body tissue through the use of a bioadhesive polymer can significantly improve the performance of many drugs[2].

Mechanism of mucoadhesion

The mechanism of mucoadhesion is generally divided into two steps

1. Contact stage
2. Consolidation step.

Contact stage: It explains the contact between the mucoadhesive polymer and the mucus membrane, with spreading and swelling of the formulation.

Consolidation step: It explains the activation and bonding of Mucoadhesive material. The mucoadhesive materials are activated by the presence of moisture. Moisture plasticizes the system, allowing the mucoadhesive molecules to break free and to link up by weak vander Waals and hydrogen bonds [3].

Mucoadhesion theories

Mucoadhesion is a complex process and numerous theories have been proposed to explain the mechanisms involved[12-13].

These theories include.

1. Wetting theory
2. Diffusion theory
3. Mechanical theory
4. The electronic theory
5. The adsorption theory
6. Cohesive theory

- **The wetting theory:** It explains the contact angle of liquids on the substrate surface is lower, then there is a greater affinity for the liquid to the substrate surface.
- **The diffusion theory:** Due to the presences of polymeric chains on the substrate surfaces, across the adhesive interface thereby forming a networked structure.

- **The mechanical theory:** It explains the diffusion of the liquid adhesives into the micro-cracks and irregularities present on the substrate surface thereby forming an interlocked structure which gives rise to adhesion.
- **The electronic theory:** Due to the transfer of electrons amongst the surfaces resulting in the formation of an electrical double layer, giving rise to attractive forces.
- **The adsorption theory:** Due to the presence of intermolecular forces (hydrogen bonding) and Vander Waal' forces, results in adhesive interaction amongst the substrate surfaces.
- **The cohesive theory:** The phenomena of bioadhesion are mainly due to the intermolecular interactions amongst like-molecules.

Based on these theories, the process of bioadhesion can be broadly classified into two categories,

1. **Chemical method**(electronic and adsorption theories)
2. **Physical method**(wetting, diffusion and cohesive theory)

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 visco elastic fluid. 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 due to the presences of mucin glycoprotein 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 visco elastic nature of the mucus.

Factors important to mucoadhesion

The bioadhesive power of a polymer is affected by the nature of the polymer and also by the nature of the surrounding media.

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.

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.

3. Physiological Variables

(a) Mucin Turnover

The natural turnover of mucin molecules is important for at least two reasons. First, the mucin turnover is expected to limit the residence time of the mucoadhesive on the mucus layer. If the adhesive strength is high, mucoadhesive are detached from the surface due to mucin turn over. Second, mucin turnover results in substantial amounts of soluble mucin molecules. These molecules interact with the mucoadhesive before they have a chance to interact with the mucus layer. Mucin turnover may depend on other factors such as presence of food.

(b) Disease States

The physiochemical properties of mucus are known to Change during disease conditions such as common cold, gastric ulcers, and ulcerative colitis, and cystic fibrosis, bacterial and fungal infections of the female reproductive tract.

Mucoadhesive polymers

Mucoadhesive polymers are water-soluble and water insoluble polymers, which are swellable networks, jointed by cross-linking agents by the processes such as wetting, mutual adsorption and interpenetration of polymer and mucus. Mucoadhesive polymers that adhere to the mucin-epithelial surface can be conveniently divided into three broad classes

1. Polymers that become sticky when placed in water and owe their mucoadhesion to stickiness.

2. Polymers that adhere through nonspecific, non-covalent interactions that are primarily electrostatic in nature (although hydrogen and hydrophobic bonding may be significant).

3. Polymers that bind to specific receptor site on tile self-surface[7].

Characteristics of an ideal mucoadhesive polymers[8-9]

- The polymer and its degradation products should be nontoxic and should be nonabsorbable from the gastrointestinal tract.
- It should be non-irritant to the mucous membrane.
- It should preferably form a strong non-covalent bond with the mucin-epithelial cell surfaces.
- It should adhere quickly to most tissue and should possess some site-specificity.
- It should allow incorporation to the daily dose of the drug and offer no hindrance to its release.
- The polymer must not decompose on storage or during the shelf life of the dosage form.
- The cost of polymer should not be high so that the prepared dosage form remains competitive.

Robinson and his group using the fluorescence technique, concluded that

- Cationic and anionic polymers bind more effectively than neutral polymers.
- Poly anions are better than poly cations in terms of binding/potential toxicity, and further, that water-insoluble polymers give greater flexibility in dosage form design compared with rapidly or slowly dissolving water-soluble polymers.
- Anionic polymers with sulfate groups bind more effectively than those with carboxylic groups.
- Degree of binding is proportional to the charge density on the polymer.
- Highly binding polymers include carboxymethyl cellulose, gelatin, hyaluronic acid, carbopol, and polycarbophil.

Molecular characteristics[10-11]

The properties exhibited by a good Mucoadhesive polymer as follows,

1. Strong hydrogen bonding groups (-OH, - COOH).

2. Strong anionic charges.

3. Sufficient flexibility to penetrate the mucus network or tissue crevices.

4. Surface tension characteristics suitable for wetting mucus/mucosal tissue surface.

5. High molecular weight.

Classification Of Mucoadhesive Polymers [6-10]

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 [11]. Nineteen types of collagen molecules have been isolated, characterized, and reported in both medical and pharmaceutical applications [12-14].

Collagen has been widely used in pharmaceutical applications in drug delivery system because of its good biocompatibility, low antigenicity, and degradability upon implantation [15]. Collagen gels are one of the first natural polymers used for drug delivery and tissue engineering [16].

Gelatin:- Gelatin is a common natural polymer (water soluble polymer) or protein which is normally produced by denaturing collagen [28]. It has been used in pharmaceutical and medical applications due to its outstanding properties such as biodegradability, biocompatibility, and low antigenicity [29]. 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 [30-31-32].

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 [35-37]. 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) [38]. 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 [39-40].

Dextran :- Dextran is a natural linear polymer of glucose linked by a 1–6 linked-glucoyranoside, and some branching of 1,3 linked side-chains [53]. Dextran is synthesized from sucrose by certain lactic-acid 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) [56].

In pharmaceutics, dextran has been used as model of drug delivery due to its characteristics such as water solubility, biocompatibility, and biodegradability [57]. Dextran is a potential polysaccharide polymer that can sustain the delivery of proteins, vaccines, and drugs [62].

Chitosan :- Chitosan is a natural polycationic 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,

nontoxic [65]. 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 [71-72].

Uses: Masking of bitter taste, as a drug carrier, as a tablet excipient, delivery platform for parenteral formulations, disintegrant and tablet coating [75].

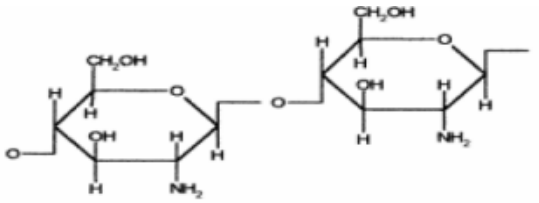

Fig.1: Chitosan

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 [80-84].

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 [85].

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 [88-90].

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 [98-102].

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

Factor affecting biodegradation of polymers:-

- Chemical structure.
- Chemical composition.
- Distribution of repeat units in multimers.
- Presents of ionic groups.
- Presence of unexpected units or chain defects.
- Configuration structure.
- Molecular weight.
- Molecular-weight distribution.
- Morphology (amorphous/semicrystalline, microstructures, residual stresses).
- Presence of low-molecular-weight compounds.
- Processing conditions.
- Sterilization process.
- Storage history.
- Shape.
- Site of implantation.
- Adsorbed and absorbed compounds (water, lipids, ions, etc.).
- Physicochemical factors (ion exchange, ionic strength, pH).
- Physical factors (shape and size changes, variations of diffusion coefficients, mechanical stresses, stress- and solvent-induced cracking, etc.).

Synthetic Polymers:-

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.

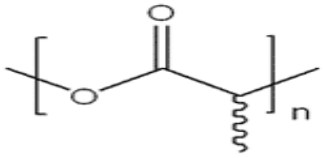

Fig. 2: General structure of PLA

Polyglycolic acid (PGA):- PGA is commonly obtained by ring-opening 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.

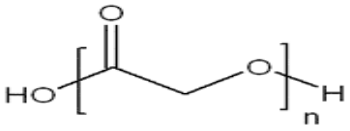

Fig. 3: General structure of PGA

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.

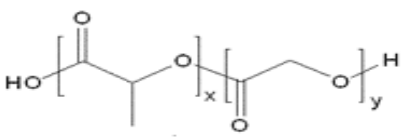

Fig. 4: General structure of PLGA

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.

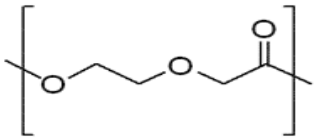

Fig. 5: General structure of PD

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).

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 sub-domains present in mucin which can substantially improve the mucoadhesive properties of the polymers.

Examples: chitosan–iminothiolane, 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 non toxic

e. Can be formulated into tablets, films, gels, microcapsules, syrups.

Evaluation of mucoadhesive drug delivery systems [80-98]

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.

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