Review Article

DRUG DELIVERY: SPECIAL EMPHASIS GIVEN ON BIODEGRADABLE POLYMERS.

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Abstract

System of administering drug through controlled delivery so that an optimum amount reaches the target site. Drug delivery system encompass the carrier, route, and target. Drug dosage forms contain many components in addition to the active pharmaceutical ingredient(s) to assist in the manufacturing process as well as to optimize drug delivery. Due to advances in drug delivery technology, excipients are currently included in novel dosage forms to fulfil specific functions and in some cases they directly or indirectly influence the extent and/or rate of drug release and absorption. Since plant polysaccharides comply with many requirements expected of pharmaceutical excipients such as non-toxicity, stability, availability and renewability they are extensively investigated for use in the development of solid oral dosage forms. Polymers have been used as a main tool to control the drug release rate from the formulations. Extensive applications of polymers in drug delivery have been realized because polymers offer unique properties which so far have not been attained by any other materials. Advances in polymer science have led to the development of several novel drug-delivery systems. These newer technological development include drug modification by chemical means, career based drug delivery and drug entrapment in polymeric matrices or within pumps that are placed in desired bodily compartments. These technical development in drug delivery/targeting approaches improve the efficacy of drug therapy thereby improve human health. Biodegradable polymers have been widely used in biomedical applications because of their known biocompatibility and biodegradability. In the biomedical area, polymers are generally used as implants and are expected to perform long term service. These improvements contribute to make medical treatment more efficient and to minimize side effects and other types of inconveniences for patients.

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Key words: Drug delivery, Biodegradable polymer, Factor Affecting Polymer.

Introduction:- Drug delivery is the method or process of administering pharmaceutical compound to achieve a therapeutic effect in humans or animals.[1,2] Drug delivery technologies modify drug release profile, absorption, distribution and elimination for the benefit of improving product efficacy, safety, as well as patient compliance and convenience.

Novel drug delivery:- A novel drug delivery system is a system that offer multiple drug delivery solutions such as:
- Oral Drug Delivery Systems and Materials
- Parenteral and Implant Drug Delivery Systems
- Pulmonary and Nasal Drug Delivery
- Transmucosal Drug Delivery
- Transdermal and Topical Drug Delivery
- Delivery of Proteins and Peptides
- Drug Delivery Pipelines
- Drug Delivery Deals

Polymers:- polymers are macromolecules having very large chains, contain a variety of functional groups, can be blended with low and high molecular weight materials. Polymers are becoming increasingly important in the field of drug delivery. Advances in polymer science have led to the development of several novel drug delivery systems. A proper consideration of surface and bulk properties can aid in the designing of polymers for various drug delivery applications.[3]. These newer technological development include drug modification...
Table 1. List of polymers used in drug delivery, [6-10]

<table>
<thead>
<tr>
<th>Type</th>
<th>Polymers</th>
</tr>
</thead>
<tbody>
<tr>
<td>a) Natural polymers</td>
<td>Polyethylene, Polypropylene, Polyamide, Polyether, Polyurethane, Polyvinyl alcohol, Polysaccharides (e.g., starch, chitosan)</td>
</tr>
<tr>
<td>b) Synthetic polymers</td>
<td>Polystyrene, Polyacrylamide, Polyurethane, Polyethylene glycol, Polyvinyl chloride, Polylactic acid, Polyanhydrides, Polyesters</td>
</tr>
<tr>
<td>c) Biodegradable polymers</td>
<td>Polyactic acid, Polylactic acid copolymer, Polyglycolic acid, Polyglycolic acid copolymer, Polyanhydrides, Polylactic acid copolymer, Polyglycolic acid copolymer</td>
</tr>
<tr>
<td>d) Non-biodegradable polymers</td>
<td>Polystyrene, Polyethylene, Polypropylene, Polyvinyl chloride, Polyvinylidene fluoride</td>
</tr>
</tbody>
</table>

by chemical means, career based drug delivery and drug entrapment in polymeric matrices or within pumps that are placed in desired bodily compartments. These technical development in drug delivery approaches improve human health. Use of polymeric material in novel drug delivery approaches has attracted the scientists.[4]

Pharmaceutical application of polymers: Used to achieve taste masking, use as a binder in tablets to viscosity and flow controlling agent in liquids, suspension and emulsions. Polymers can be used as film coating to disguise the unpleasant taste of drug and to enhance drug stability and to modify drug release characteristics.[5]

Natural polymers: are described as below:

Collagen: Collagen is a major natural protein component in mammals that is fabricated from glycine-proline-(hydroxy) proline repeats to form a triple helix molecular structure [11]. So far, 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 due to the fulfillment of many requirements of a drug delivery system such as good biocompatibility, low antigenicity, and degradability upon implantation [15]. Furthermore, collagen gels are one of the first natural polymers to be used as a promising matrix for drug delivery and tissue engineering [16]. Biodegradable collagen-based systems have served as 3D scaffold for cell culture, survival of transfected fibroblasts, and gene therapy [17, 18]. In this case, collagen scaffolds were fabricated through introducing various chemical cross-linking agents (i.e., glutaraldehyde, formaldehyde, carbodiimide) or by physical treatments (i.e., UV irradiation, freeze-drying, and heating) [19, 20-23].

Figure 1: A schematic representation of collagen-based liposome. (source: kang et al. [27]).

Example: The combination of liposomes and collagen-based technologies has been long achieved since the early 80s [16]. In this case, drugs and other bioactive agents were firstly encapsulated in the liposomes and then embedded inside a depot composed of collagen-based systems, including scaffolds and gels. The combination of these two technologies (i.e., liposomes and collagen-based system) has improved storage stability, prolonged the drug release rate, and increased the therapeutic efficacy [11, 24, 25]. In addition, a study that was conducted by Marston et al. [26], demonstrated that temperature sensitive liposomes and
collagen may thermally trigger the release of calcium and phosphate salts. Multiple collagen-based system for pharmaceutical carriers or medicinal applications are currently available for clinical purposes [27]. Figure 1 depicts a schematic representation of collagen-based liposome.

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]. In addition, gelatin can be easy to manipulate due to its isoelectric point that allows it to change from negative to positive charge in an appropriate physiological environment or during the fabrication, a property that has found it being very attractive to many pharmaceutical researchers [30]. Gelatin 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 [31, 29, 32]. It has been reported that it is possible to incorporate liposome-loaded bioactive compounds into PEG-gelatin gel which function as porous scaffold gelatin-based temporary depots with controlled drug release over prolonged periods of time [33, 34]. However, some setbacks have been identified, and they are said be associated with the use of gelatin-based systems in pharmaceutical applications. These setbacks include poor mechanical strength and ineffectiveness in the management of infected sites [12].

Albumin: Serum albumin was conjugated to poly-(ethylene glycol) (PEG) and cross-linked to form mono-PEGylated albumin hydrogels. These hydrogels were used as a basis for drug carrying tissue engineering scaffold materials, based on the natural affinity of various drugs and compounds for the tethered albumin in the polymer network.

Alginate: Alginate also serves as 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 derivatives are widely used by many pharmaceutical scientists for drug delivery and tissue engineering applications due to its many unique 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]. Since alginate is anionic, fabrication of alginate hydrogels has successively been achieved through a reaction with cross-linking agents such as divalent or trivalent cations mainly calcium ions, water-soluble carbodiimide, and/or glutaraldehyde [41]. The cross-linking methodology was conducted at room temperature and physiological pH [42]. The success in fabricating highly porous 3D alginate scaffolds has been through lyophilization [43]. Thus far, alginate-based systems have been successfully used as a matrix for the encapsulation of stem cells and for controlled release of proteins, genes, and drugs [44-48]. In addition, alginate-based systems have been used as depots for bioactive agent-loaded liposomes, for slow drug release [49, 50]. Highly increased efficacy has been reported from these integrated delivery systems when compared to polymeric-based systems or liposome-based systems alone [51,52].

Dextran: Dextran is a natural linear polymer of glucose linked by a 1→6 linked-glucopyranoside, 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) (Rhemacrodex) and dextran 70 Kilodaltons (kDa) (Macrodex) [54,55]. In pharmaceutics, dextran has been used as model of drug delivery due to its unique characteristics that differentiate it from other types of polysaccharide. This include water solubility, biocompatibility, and biodegradability [56]. In recent studies, dextran has been regarded as a potential polysaccharide polymer that can sustain the delivery of both proteins, vaccines, and drugs [57-60]. Interleukin-2, which is a highly effective anticancer drug, is among the success obtained in delivering a combination of drug-loaded liposome and injectable dextran hydrogel [61]. Injectable and degradable dextran-based systems for drug delivery were generated by a cross-linking reaction with photo-polymerization or free radical polymerization [62].

A study by Stenekes and coworkers [63] demonstrated the successive encapsulation of a drug-loaded liposome depot into a dextran polymer-based material. The polymeric-based materials were fabricated using a two phase system, the first phase was water and poly(ethylene glycol) and the second one water methacyrlylated dextran. The slower degradation of dextran polymeric material resulted in sustained liposome release over a period of 100 days [63]. Liposomes released from depot were reported to be intact, and there was no significant change in liposomal size. In a gene therapy study by Liptay and coworkers [64], it was reported that recombinant DNA (which contains chloramphenicol acetyltransferase) was successively encapsulated in cationic liposomes and then integrated within dextran. This system was reported to be a suitable delivery system since it could stop transfection efficiency within the colon epithelium wall in vivo [64].
**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 application. As a pharmaceutical excipient, chitosan has been used in many formulations like powders, tablets, emulsions and gels. Furthermore a controlled release of incorporated drugs can be guaranteed.[66, 67]. Chitosan also shows mucoadhesive properties and antimicrobial properties.[68,69]. The bitter taste of natural extracts such as caffeine has been masked using chitosan. Chitosan can potentially be used as a drug carrier, a tablet excipient, delivery platform for parenteral formulations, disintegrant and tablet coating. From toxicity and safety point, lower molecular weight chitosan (as an oligosaccharide) has been shown to be safer with negligible cytotoxicity on coca-2-cell. During the encapsulation process using synthetic polymers, the protein is generally exposed to the conditions which might cause their denaturation or deactivation. Therefore a biocompatible alternative such as chitosan is desirable for such applications. Gels based on chitosan and ovalbumin protein have been suggested for pharmaceutical and cosmetic use. Chitosan can also be mixed with nonionic surfactant such as sorbitan ester to make emulsion like solution s or creams.[70]. It is a promising bioadhesive material at physiological pHs. This polymer possesses OH and NH2 group that can give rise to hydrogen bonding. These properties are considered essential for mucoadhesion.[71, 72]. One study accounts for possible use of chitosan in mixtures of different ratios with anionic polymers for the preparation of mucoadhesive tablets to be used as a vaginal delivery system for metronidazole [73]. By the introduction of thiol groups to chitosan the mucoadhesive properties could be strongly improved while maintaining its biodegradability [74]. Chitosan was thereby modified by attaching thioglycolic acid (TGA) onto the primary amino groups of the polymer via an amide bond formation [75]. The excellent bioadhesion could result in an increased residence time of a drug at the site of absorption by interacting with the mucosa [76, 77]. As chitosan is also known to exhibit antimicrobial activity the chitosan-TGA conjugate would be ideal as a matrix for the mainly cationic antimycotics for treating mycotic infections in the vagina. A common microbial problem in the vulvovaginal tract is the infection with C. albicans [78]. Approximately 75% of women will have a vaginal infection with a Candida strain during their life and about 40–50% of them will suffer a second one and a small percentage will show a chronic course [79]. By the introduction of thiol groups the bioadhesive properties of chitosan could be significantly improved. The addition of clotrimazole led thereby to a further increase in bioadhesion on mucosal tissue.

**Cellulose Derivatives**: Cellulose is the most abundant naturally occurring biopolymer [80, 81]. Various natural fibers such as cotton and higher plants have cellulose as their main constituent [82, 83]. 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 [81]; the poor solubility is attributed primarily to the strong intramolecular and intermolecular hydrogen bonding between the individual chains [80]. In spite of its poor solubility characteristics, cellulose is used in a wide range of applications including composites, netting, upholstery, coatings, packing, paper, etc. Chemical modification of cellulose is performed to improve process ability and to produce cellulose derivatives (cellulosics) which can be tailored for specific industrial applications [84]. Large scale commercial cellulose ethers include carboxymethyl cellulose (CMC), methyl cellulose (MC), hydroxyethylcellulose (HEC), hydroxypropyl methyl cellulose (HPMC), hydroxypropyl 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. Being a biodegradable polymer with well-defined chemical properties, it has a huge potential as a versatile renewable resource for various material applications in food and nonfood areas. The composition and properties of commercial available starches have been studied extensively. 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 amyllopectin. 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, amyllopectin is a highly branched molecule with a molecular weight of 107-109 g mol-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.
Modified starch was tested for general applicability of a new pregelatinized starch product in directly compressible controlled-release matrix systems. It was prepared by enzymatic degradation of potato starch followed by precipitation (retrogradation), filtration and washing with ethanol. The advantages of the material include 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. Release rates from retrograded pregelatinized starch tablets can be enhanced or decreased to the desired profile by different parameters like geometries of the tablet, compaction force and the incorporation of additional excipients [85].

**Hyaluronic acid:** Hyaluronic acid (also called as Hyaluronan and Hyaluronate (HA) and Sodium Hyaluronate(SA) is sodium salt form of hyaluronic acid) is a biodegradable, biocompatible, and viscoelastic linear polysaccharide of a wide molecular weight range (1000 to 10,000,000 Da). It is a naturally occurring biopolymer, which serves important biological functions in bacteria and higher animals including humans. Naturally occurring hyaluronic acid may be found in the tissue of higher animals, particularly as intercellular space filler. It is found in greatest concentrations in the vitreous humor of the eye and in the synovial fluid of articualr joints. [86]. Hyaluronic acid comprises linear, unbraniching, polyanionic disaccharide units consisting of glucuronic acid (GlcUA) and N-acetyl glucosamine (GlcNAc) joined alternatingly by β-1-3 and β-1-4 glycosidic bonds. Hyaluronic acid solutions are characteristically viscoelastic and pseudoplastic. 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. As a microcapsule, it can be used for targeted drug delivery. [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. However, in colon, they undergo fermentation in the presence of vast colonic microfloras into small monosaccharide and thus absorbed from these regions. [88, 90] β-cyclodextrins are degraded to a very small extent in the small intestine but are completely digested in the large intestine. Most bacterial strains found abundantly in human beings are capable of degrading cyclodextrins polysaccharide.

**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 [90]. Polymers within this group retain their properties for a
limited period of time and then gradually degrade into soluble molecules that can be excreted from the body [91].

Biodegradable polymers are preferred for drug delivery applications, since the need for surgical removal of the depleted device is eliminated. Although the number of biodegradable polymers is large, only a limited number of polymers is suitable for drug delivery applications. Suitable candidates must not only be biodegradable but also fit the high prerequisites of biocompatibility. In addition, a polymer should ideally offer processability, sterilizability, and storage stability if it is to be useful for biomedical applications [92]. The greatest advantage of degradable polymers is that they are broken down into biologically acceptable molecules that are metabolized and removed from the body via normal metabolic pathways. However, biodegradable materials do produce degradation by-products that must be tolerated with little or no adverse reactions within the biological environment. These degradation products—both desirable and potentially non desirable—must be tested thoroughly, since there are a number of factors that will affect the biodegradation of the original materials. The most important of these factors are shown in the box below—a list that is by no means complete, but does provide an indication of the breadth of structural, chemical, and processing properties that can affect biodegradable drug delivery systems.

**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.
- Annealing.
- 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-induced and solvent-induced cracking, etc.).

Biodegradable polymers mainly investigated for drug delivery applications are of either natural or synthetic origin.

**Natural polymers,** already we have discussed above.

**Synthetic Polymers:**

- Polyester:

  1. **Polylactic acid (PLA):** PLA is thermoplastic biodegradable polymer produced synthetically by polymerization of lactic acid monomers or cyclic lactide dimmers. Lactic acid is produced by fermentation of natural carbohydrates for example, maize or wheat or waste products from the agricultural or food industry. Commercial quantities of PLA for packaging applications are produced through ring opening polymerization of lactide, a reaction favoring the formation of high molecular polymers. The final crystallinity and mechanical properties of the polymer depends on the stereochemistry of polymer backbone. 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’. PLA does not degrade by microbial attack.

  PLA is currently used in loose fill packaging, food packaging films, thermoformed containers and short shelf life bottles. PLA can be laminated to paper and paperboard by extrusion coating for further use as packaging material. Drinking cups and food containers for short shelf life products are other application areas. Fabrics produced from PLA provide a silky feel, durability, and moisture-management properties. PEA is useful for producing compost bags and disposable tableware also. PLA has number of biomedical applications, such as sutures, stents, dialysis media and drug delivery devices. General structure of PLA as shown in fig. 3

  ![Figure:3](image)
II). Polyglycolic acid (PGA):- PGA is commonly obtained by ring-opening polymerization of the cyclic diester of glycolic acid, glycolide [93,94]. PGA is a hard, tough, crystalline polymer with a melting temperature of 225 °C and a glass transition temperature, Tg, of 36 °C [93]. Unlike closely related polyesters such as PLA, PGA is insoluble in most common polymer solvents [93]. PGA has excellent fiber-forming properties and was commercially introduced in 1970 as the first synthetic absorbable suture under the trade name Dexon™ [93]. 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. General structure of PGA is shown in fig. 4

![Figure 4](image)

III). 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. The polymer is primarily a product of carbon assimilation (from glucose or starch) and is employed by microorganisms as a form of ‘energy storage molecule’ to be metabolized when other common energy sources are not available. PHB and its copolymers have attracted much attention because they are produced biosynthetically from renewable resources. Microcapsules from PHB have been prepared by various techniques and investigated for the release of bovine serum albumin [95]. PHB has also been suggested as a suitable matrix for drug delivery in veterinary medicine, for instance in the rumen of cattle [96].

IV). Poly(lactide-co-glycolide), PLGA:- Among the copolyesters investigated, extensive research has been performed in developing a full range of PLGA polymers. Both L- and DL-lactides have been used for copolymerization. The ratio of glycolide to lactide at different compositions allows control of the degree of crystallinity of the polymers. [97]. When the crystalline PGA is copolymerized with PLA, the degree of crystallinity is reduced and as a result this leads to increases in rates of hydration and hydrolysis. It can therefore be concluded that the degradation time of the copolymer is related to the ratio of monomers used in synthesis. In general, the higher the content of glycolide, the quicker the rate of degradation. However, an exception to this rule is the 50:50 ratio of PGA: PLA, which exhibits the fastest degradation. [98, 99]. PLGA is used in drug delivery applications. Non-steroidal anti-inflammatory drugs, e.g., difusilin [100] and diclofenac sodium [101, 102], have been incorporated into PLGA microspheres and investigated for the treatment of rheumatoid arthritis, osteoarthritis, and related diseases. The encapsulation of bio macromolecules, e.g., proteins and vaccines, into polymeric microspheres presents a formidable problem because of the delicacy of these agents; bioactivity might be lost during preparation, and the release may be poor due to adsorption and/or aggregation. For instance, the release of recombinant human interferon-g from PLGA microspheres was incomplete and the instability of the system limited its use to 7 days or less [103]. Similarly, incomplete release of lysozyme, recombinant human growth hormone, and a nerve growth factor from PLGA microspheres was reported [104, 105, 106]. Hence, much effort has been spent in evaluating PLGA delivery systems, with special regard to microsphere preparation, protein stability, and release characteristics. Model proteins studied include bovine serum albumin, lysozyme, transferrin, and trypsin [107, 104, 108]. Several peptides, including vapreotide and rismorelin porcine, have been successfully incorporated and released from PLGA microspheres [109–111]. Systems for the controlled release of antigens have a great potential as vaccine adjuvants [112, 113, 108]. Recently, several studies of controlled release systems for DNA have been presented. DNA of different sizes has successfully been incorporated into PLGA microspheres but the loss of DNA integrity and activity still remains an important issue to be solved for these systems [114, 115-117]. General structure of PLGA is shown in fig. 5

![Figure 5](image)

V). Poly(e-caprolactone), PCL:- PCL is obtained by ring-opening polymerization of the 6-membered lactone, e-caprolactone (e-CL). Anionic, cationic, coordination, or radical polymerization routes are all applicable [118]. Recently, enzymatic catalyzed polymerization of e-CL has been reported [119, 120]. PCL crystallizes readily due to the regular structure and has a melting temperature of 61 °C. It is tough and flexible [118]. The Tg of PCL is low (~60 °C). Thus, PCL is in the rubbery state and exhibits high permeability to low molecular species at body temperature. These properties, combined with documented biocompatibility, make PCL a promising candidate for controlled release applications [121]. PCL degradation proceeds through hydrolysis of backbone ester bonds as well
as by enzymatic attack. Hence, PCL degrades under a range of conditions, biotically in soil, lake waters, sewage sludge, in vivo, and in compost, and abiotically in phosphate buffer solutions [122-125]. Hydrolysis of PCL yields 6-hydroxycaproic acid, an intermediate of the o-oxidation, which enters the citric acid cycle and is completely metabolized. Hydrolysis, however, proceeds by homogeneous erosion at a much slower rate than PLA and PLGA [125]. Hydrolysis of PCL is faster at basic pH and higher temperatures [118]. PCL hydrolyzes slowly compared to PLA and PLGA, it is most suitable for long-term drug delivery. Capronor®, a 1-year contraceptive represents such a system [118].

VI. Polydioxanone(PDS):- Although biodegradable polylactides and glycolides have been used to develop versatile resorbable multi-filament structures, there is growing research involved in the development of materials that form monofilament sutures. Multifilament sutures have a higher risk of infection associated with their use and cause a greater amount of friction when penetrating tissues. [126, 127]. Polydioxanone (referred to as PDS) is made by a ring-opening polymerization of thep-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 and also has a lower modulus than PLA or PGA. For the production of sutures, PDS is generally extruded into fibers at the lowest possible temperature, in order to avoid its spontaneous depolymerization back to the monomer. General Structure of Polydioxanone is shown in figure 6

![Polydioxanone](image)

**Figure:** 6

- **Polyanhydrides:-** Poly anhydride 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. An example of the polymer structure is shown in Figure 7. These compounds contain two types of important bonds - anhydride and ester bonds shown in Figure 7 in blue and red respectively. In the presence of water, both bonds may degrade hydrolytically, releasing salicylic acid (B) and sebacic acid (C). Salicylic acid (B) is the active form of aspirin, an anti-inflammatory agent, and sebacic acid is currently used in drug delivery systems (Brem et al., 1995). In vivo mice studies have indicated that this polymer assists in wound healing and that it promotes bone growth (Macedo, 1999).

The release of salicylic acid (B) via bond hydrolysis opens up a variety of possibilities for creating drug delivery systems. Potential applications include treatment of inflammatory bowel disease, dental implants, and tissue scaffolding. The studies on the degradation rate, the rate of release of salicylic acid as a function of pH, have shown that this polymer takes three months to degrade in acidic and neutral environment, but at basic pH it degrades in 19-40 hours (Erdmann and Uhlich, 1999). Since the upper gastrointestinal tract is acidic or neutral, this polymeric drug can reach the intestines undamaged, and release salicylic acid directly to the lower intestinal tract to treat the disease. Aspirin is also used in dentistry, for example, in cases of tooth breakage when there cannot be an immediate operation. In this procedure, the fast influx of salicylic acid irritates the surrounding tissue. Slower release of the medication, provided by the poly(anhydride-esters) would be a gentler solution.

A drawback to the poly(anhydride-ester) structure shown in Figure 7 is its low T_g (glass transition temperature). This is a temperature at which a polymer goes from a solid into a rubbery state. The T_g of this polymer is several degrees below body temperature (37 °C), which means that it becomes a soft, sticky material when placed in the body. Because the polymer is being developed for use as a suture material, it is undesirable for the polymer to become soft during the suturing process. Therefore, poly(anhydride-esters) with T_g's higher than body temperature need to be developed [128, 129]

- **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 (Kiely et al.,1994; Gaymans and Sikkema, 1999; Hopf, 2001). A typical 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 that are
valuable because of their superior physicochemical and physicomechanical properties such as abrasion resistance, chemical inertness, relatively high modulus, minimal degradation, ease of processing, thermo plasticity, higher melting points and heat resistance than many other semi-crystalline polymers such as polyethylene (Makino et al., 1990; Kiely et al., 1994; Chattaraj et al., 1995; Jones et al., 1997; Gaymans and Sikkema, 1999; Murthy, 1999; Ostad and Gard, 2000; Hopf, 2001; Li et al., 2001; Sikorski et al., 2001; Ostad et al., 2002; Fornes et al., 2003; Cui and Yan, 2005).

The aforementioned physical properties as well as the extensive clinical use of the synthetic aliphatic polyamides as surgical sutures (Van, 1996; Lundborg et al., 1997; Dolorico et al., 2003; Lee et al., 2003; Seitz et al., 2003; Lai, 2004) demonstrates their biocompatibility and non-toxicity and make them attractive for use in the design and development of drug delivery systems.

**Phosphorous based derivatives:**

1). Polyphosphazenes:- It consists of phosphorous atoms attached to either carbon or oxygen. Polyphosphazenes, another new class of polymer are being investigated for delivery of proteins[130]. The uniqueness of this class of polymer lies in the chemical reactivity of phosphorous which enables a wide range of side chains to be attached for manipulating the biodegradation rates and the molecular weight of polymer.[131].
Poly orthoesters: Poly(orthoester)s (POE) are another family of polymers identified as degradable polymers suitable for orthopaedic applications. Heller and coworkers reported on the synthesis of a family of polyorthoesters (Figure 6) that degrades by surface erosion (Ng et al., 1997). With the addition of lactide segments as part of the polymer structure, tunable degradation times ranging from 15 to hundreds of days can be achieved. The degradation of the lactide segments produces carboxylic acids, which catalyze the degradation of the orthoester (Ng et al., 1997). Preliminary in-vivo studies have shown that POE (Figure 6) to increase bone growth in comparison with poly(dilactide-co-glycolide) (Andriano et al., 1999).

Conclusion: Biodegradable polymers have proven their potential for the development of new, advanced and efficient drug delivery systems. They are capable of delivering a wide range of bioactive materials. Today the stress is on patient compliance and to achieve this objective there is spurt in development of NDDS. As the herbal excipients are promising biodegradable materials, these can be chemically compatible with the excipients in drug delivery systems. In addition herbal excipients are non-toxic, freely available, and less expensive compared to their synthetic counterparts. They have a major role to play in pharmaceutical industry. Therefore, in the years to come, there is going to be continued interest in the natural excipients to have better materials for drug.

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