POLYMERS FOR DRUG DELIVERY SYSTEM: A REVIEW

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Abstract

Pharmaceutical invention and research are now increasingly focusing on delivery systems which enhance desirable therapeutic objectives while minimizing side effects. Drug delivery systems, ranging from implantable electronic devices to single polymer chains, are required to be compatible with processes in the body (biocompatibility) as well as with the drug to be delivered. DDS alter the bio-distribution and pharmacokinetics of the associated drug: that is the time-dependent percentage of the administered dose in the different organs of the body. There are various natural and synthetic polymers are used in drug delivery system. The present communication focuses all these aspects with emphasizes of various polymers used in various drug delivery systems.

Key-words: Polymers, Drug delivery system, Biodegradable polymers

Introduction

Humankind's efforts to confront disease dates back to early civilization. Substances taken from nature were tested and used to treat dysfunctions of physiological life processes, pain and discomfort. With the advancement of science, the active ingredients of these materials, the drugs, were identified, isolated and their mechanism of action elucidated. Drug activity is a result of molecular interaction(s) in certain cells & therefore it is necessary for the drug to reach somehow the site of action following administration (oral, intravenous, local, transdermal, etc.) at sufficient concentrations. The scientific field dealing with this issue is known as drug delivery and has essentially the following aim: to deliver the drug at the right place, at the right concentration for the right period of time. When this is impossible by simply selecting an appropriate administration route, or if such administration causes patient discomfort, strategies based on the association of the drug with a carrier (a drug delivery system – DDS) are an alternative.[1-2]

Pharmaceutical invention and research are now increasingly focusing on delivery systems which enhance desirable therapeutic objectives while minimizing side effects.[3] Carrier-mediated drug delivery has emerged as a powerful methodology for the treatment of various pathologies. The therapeutic index of traditional and novel drugs is enhanced via the increase of specificity due to targeting of drugs to a particular tissue, cell or intracellular compartment, the control over release kinetics, the protection of the active agent or a combination of the above.[4-5]

Drug delivery systems, ranging from implantable electronic devices to single polymer chains, are required to be compatible with processes in the body (biocompatibility) as well as with the drug to be delivered. DDS alter the biodistribution and pharmacokinetics of the assosciated drug: that is the time-dependent percentage of the administered dose in the different organs of the body. Furthermore, obstacles arising from low drug solubility, degradation (environmental or enzymatic), fast clearance rates, non-specific toxicity, inability to cross biological barriers, just to mention a few, may be addressed by DDS.[2]

Overall, the challenge of increasing the therapeutic effect of drugs, with a concurrent minimization of side effects, can be tackled through proper design and engineering of the DDS, in a case-to-case manner.[1, 5] There are various routes for drug delivery: Oral, Inject-able, Mucosal, Trans-dermal, Ocular, aginal/Anal, Needle, Needle-less, Nasal, Buccal, Pulmonary, Active, Passive and Topical.

Polymer

A polymer is a large molecule (macromolecule) composed of repeating structural units typically connected by covalent chemical bonds. Natural polymers (from the Greek poly meaning "many" and meros meaning "parts") are found in many forms such as horns of animals, tortoise shell, shellac (from the lac beetle), rosin (from pine trees), asphalt, and tar from distillation of organic materials. One of the most useful of the natural polymers was rubber, obtained from the sap of the hevea tree. Other natural polymers are cellulose, chitosan, hyluronic acid derivatives, etc.[6-18]

Types of Natural Polymers

The natural polymers obtained from nature are known as natural polymers. There are five types available in natural polymers.

- Starch
- Cellulose
- Proteins
- Nucleic Acid
- Natural rubber

Starch: It is a polymer of glucose. It is a principal food store of plants.

Cellulose: It is also polymer glucose. It is principal structural material of the plants. Both starch and cellulose are produced by plants through photosynthesis.

Proteins: These are polymers of alpha amino acids. They have usually 20 to 100 alpha amino acids joined together in a highly organized arrangement. These are building group of animals.

Nucleic Acids: These are polymers has a variety of nucleotides. RNA and DNA are ordinary nucleotides.

Natural rubber: It is a polymer of unsaturated hydrocarbon, 3 butadiene known as isoprene. It is finding from latex of rubber trees.

Biopolymers such as proteins and nucleic acids play crucial roles in biological processes. A variety of other natural polymers exist, such as cellulose, which is the main constituent of wood and paper.

Polymer properties

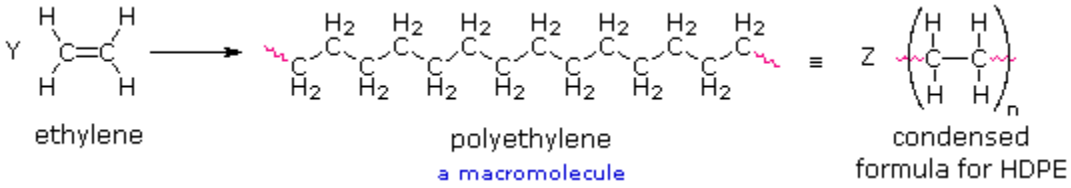
Polymer properties are broadly divided into several classes:

1. the identity of its constituent monomers.
2. microstructure, describe the arrangement of these monomers within the polymer at the scale of a single chain. These basic structural properties play a major role in determining bulk physical properties of the polymer, which describe how the polymer behaves as a continuous macroscopic material.
3. chemical properties, at the nano-scale, describe how the chains interact through various physical forces. At the macro-scale, they describe how the bulk polymer interacts with other chemicals and solvents.

Types of polymers

- Polymers that contain only a single type of repeat unit are known as homopolymers, for example, Poly(styrene) is composed only of styrene monomer residues, and is therefore classified as a homopolymer
- Polymers containing a mixture of repeat units are known as copolymers, for example, Ethylene-vinyl acetate contains more than one variety of repeat unit and is thus a copolymer.

A polymer molecule containing ionizable subunits is known as a polyelectrolyte or ionomer. For example polyethylene as shown in figure:



Polymers are further classified by the reaction mode of polymerization, these include:

Addition Polymers - the monomer molecules bond to each other without the loss of any other atoms. Alkene monomers are the biggest groups of polymers in this class.

Condensation Polymers - usually two different monomer combine with the loss of a small molecule, usually water. Polyesters and polyamides (nylon) are in this class of polymers. Polyurethane Foam in graphic.

Classification based upon the physical property related to heating:

Thermoplastics - plastics that soften when heated and become firm again when cooled. This is the more popular type of plastic because the heating and cooling may be repeated.

Thermosets - plastics that soften when heated and can be molded, but harden permanently. They will decompose when reheated. An example is Bakelite, which is used in toasters, handles for pots and pans, dishes, electrical outlets and billiard balls.

Advantages

The greatest advantage of these 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. Common classes of polymers used to encapsulate drugs in colloidal systems include polyamides, poly(amino acids), polyesters, polyorthoesters and polyanhydrides.

Biodegradable polymers [19-33]

To be successfully used in controlled drug delivery formulations, a material must be chemically inert and free of leachable impurities. It must also have an appropriate physical structure, with minimal undesired aging, and be readily processable.

Example:

- Poly(urethanes) for elasticity.
- Poly(siloxanes) or silicones for insulating ability.
- Poly(methyl methacrylate) for physical strength and transparency.
- Poly(vinyl alcohol) for hydrophilicity and strength.
- Poly(ethylene) for toughness and lack of swelling.
- Poly(vinyl pyrrolidone) for suspension capabilities.

Some of the materials that are currently being used or studied for controlled drug delivery include

- Poly(2-hydroxy ethyl methacrylate).
- Poly(N-vinyl pyrrolidone).
- Poly(methyl methacrylate).
- Poly(vinyl alcohol).
- Poly(acrylic acid).
- Polyacrylamide.
- Poly(ethylene-co-vinyl acetate).
- Poly(ethylene glycol).
- Poly(methacrylic acid).

However, in recent years additional polymers designed primarily for medical applications have entered the arena of controlled release. Many of these materials are designed to degrade within the body, among them

- Polylactides (PLA).
- Polyglycolides (PGA).
- Poly(lactide-co-glycolides) (PLGA).
- Polyanhydrides.
- Polyorthoesters.

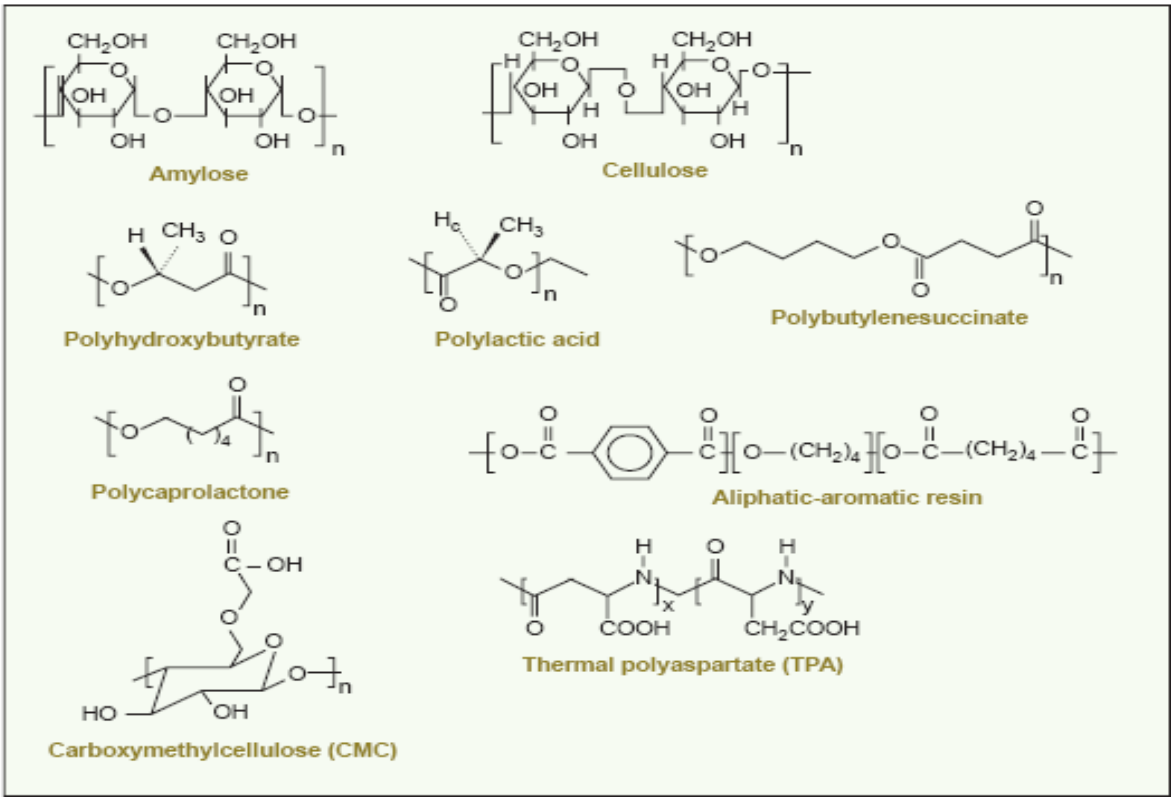


Fig. 1: Structures of selected biodegradable polymers

Polyacryaltes and poly (acrylic acid):

In most of the vaginal preparations poly (acrylic acid) (PAA) derivatives have been used as mucoadhesive polymer as it has been considered as good mucoadhesive. Among all PAA derivatives in most of the vaginal preparations, either carbopol or polycarbophil has been used as mucoadhesive polymer.

Polycarbophil is a lightly cross-linked PAA. Polycarbophil gel is able to alter vaginal and suburethral blood flow favourably from the surface of the vaginal tissue, which leads to significant improvement in dry vagina and menopause related stress incontinence.

Example: Metronidazole tablets in a modified starch-polyacrylic acid mixture showed an increased potential for curing bacterial vaginosis in women.

Carbopols which are very high molecular weight polymers of acrylic acid, have been used mainly for its mucoadhesive properties in vaginal drug delivery systems. Carbopol is used in formulation of the mucoadhesive polymeric films developed as female controlled drug delivery system (FcDDS). It was found that, carbopol is able to not only increase the degree of hydration and mucoadhesiveness, but also maintain the morphology of the films in the vaginal cavity8. The ability of carbopol gel to attach to lymphocytes also makes them a site-specific drug delivery system for AIDS prophylaxis.

Cellulose derivatives:

Various cellulose derivatives like hydroxy ethylcellulose (HEC), hydroxy propyl cellulose (HPC), hydroxy propyl methyl cellulose (HPMC), methyl cellulose (MC), sodium carboxy methylcellulose (Sod CMC) etc have been studied for intravaginal drug delivery systems. Among all the cellulose derivatives, Sod CMC are used in New drug delivery system.

Gynol II, a contraceptive jelly, contains sodium carboxymethylcellulose as a mucoadhesive polymer and is used as a spermicidal contraceptive in conjunction with barrier methods of contraception. HPMC and HEC was also evaluated as mucoadhesive polymer in the formation of the bioadhesive vaginal films of sodium polystyrene sulfonate (PSS), a novel contraceptive antimicrobial agent. In the study of bioadhesive acyclovir vaginal tablets, the units were prepared by using PAA, MC, CMC, HPC and HPMC as bioadhesive polymers in different concentrations by direct compression as well as wet granulation techniques. It was found that, swelling of the tablets containing HPC, CMC and MC was very rapid and caused disintegration of the tablets. The swelling behavior of the tablets containing HPMC lasted six hours in lactic acid solution. The maximal detachment force from the vaginal tissue was found to depend on the concentration and type of the bioadhesive polymer. The tablets containing HPMC needed the highest detachment force.

Chitosan:

Partial deacetylation of chitin results in the production of chitosan, which is a polysaccharide comprising copolymers of glucosamine and N-acetyl glucosamine. Chitosan is cationic polyamine with a high charge density at pH<6.5, so adhere to negatively charged surfaces. It is also known to exhibit antimicrobial activity.

Chitosan is use in pharma and medicine particularly because of its penetration enhancement capability, alongside with other intrinsic properties such as biocompatibility, biodegradability, bioadhesivity, and bacteriostatic effects. It was found that, chitosan citrate possess potential properties of penetration enhancement and protease inhibition. By introducing the thiol group on the chitosan, it was found that bioadhesiveness of the chitosan could be significantly increased. In Clotrimazole therapy, controlled release of the Clotrimazole was found to be depending on the amount of the covalently attached thiol group.

Hyaluronic acid and derivatives:

Sodium hyaluronate is the predominant form of hyaluronic acid at physiological pH. It is most common negatively charged glycosaminoglycan in the human vitreous humor. In its natural form, hyaluronic acid exists as a high molecular weight polymer of 106-107 Da. Microspheres prepared from hyaluronic esters have been evaluated for treatment of postmenopausal osteoporosis. One of the patent revealed that the combination of hyaluronic acid and HEC can be used to minimise the vaginal dryness to some extent.

Sodium alginate:

Sodium alginate consists of the sodium salt of alginic acid, which is a mixture of polyuronic acid composed of residue of D-mannuronic and L- guluronic acid. The adhesiveness of the hydrogel of sod alginate has been investigated and it is found that adhesiveness increases with concentration. Alginate crosslinked with calcium chloride containing three percent N-9 were manufactured over a pH range of 3.4-5.9 and at different osmolarity. It was found that delivery gel pH had a significant effect on spermicidal efficacy of the alginate-N9 system; biodiffusion increased with decreasing pH23.

Poly vinyl alcohol (PVA)

PVA is water soluble synthetic polymer represented by the formula (C2H4O) n. The value of n for commercially available materials lie between 500 and 5,000, equivalent to a molecular weight (MW) range of approximately 20,000- 200,00014.

In the development of the bioadhesive films of PSS, effect of MW of PVA on physical and mechanical properties of films was studied using three different grades, viz low MW (30,000-70,000), medium MW (89,000-98,000), and high MW (125,000). Films obtained with all the three grades possessed good peelability, flexibility and physical and mechanical properties. Bioadhesive strength of PSS films were compared with commercial products VCF and Ortho-Option and it was found significantly greater for PSS films.

Poloxamers or Pluronics:

The amphiphilic poly(ethylene glycol)-bl-poly(propylene glycol)-bl-poly(ethylene glycol) polymers, known as Poloxamers or Pluronics, have attracted significant attention for controlled drug delivery applications in the form of micellar nanocontainers and physical gels. Hydrophobic self-assembly between the central PPG blocks induces polymer assembly into 5-20 nm spherical structures, consisting of a hydrophobic PPG-rich core stabilized by a hydrophilic PEG-rich corona. The core may solubilize lipophilic molecules, and the hydrated PEG corona prevents aggregation, protein adsorption, and recognition of the micelles as foreign bodies by the immune system. Low toxicity and weak immunogenic properties have allowed for the use of Pluronic in topical and systemic administration including intravenously administered micellar formulations that have reached the level of clinical trials.

Polyesters:

Recently, biodegradable polyesters such as poly (lactic acid), poly (glycolic acid) and the copolymers of lactic and glycolic acid, i.e., poly (lactide-co-glycolide). (PLGA) have been used extensively for biomedical applications. Being biodegradable they have the advantage of not requiring surgery for removal afterthey have served their purposes. They protect the entrapped drug against degradation and control its site specific delivery.

Synthesis: They are synthesised through ring opening polymerisation of cyclic lactones. These are copolymers with varying lactide: glycolide ratios.

Properties: These copolymers are amorphous and easily dissolve in organic solvents such as dichloromethane and ethyl acetate. The degradation rate in water is a function of the molecular

weight and the lactide:glycolide ratio. . Higher glycolide content and lower molecular weight increase the degradation rate. As they are all strongly hydrophobic they are more efficient for encapsulation of hydrophobic drugs than hydrophilic drugs.

Poly (Ethylene glycol) based Co Polymers

Several types of surface modified nanoparticles have been described recently. The most common moiety used for surface modification is poly (ethylene glycol) (PEG). PEG is a hydrophilic, non-ionic polymer that has been shown to exhibit excellent biocompatibility. PEG molecules can be added to the particles via covalent bonding or by surface adsorption.

Advantages : The presence of a PEGbrush on the surface of nanoparticles besides increasing residence time in the systemic circulation can also reduce protein and enzyme adsorption on the surface and thus can retard particle degradation. The degree of protein adsorption can be minimized by altering the density and molecular weight of PEG on the surface. The stability of PLA particles has been shown to increase in simulated gastric fluid (SGF) with the addition of PEG on the particle surface.

After 4 hours in Simulated Gastric Fluid, 9% of the PLA nanoparticles converted to lactate versus 3% conversion for PEG-PLA particles. PEG is also believed to facilitate transport through the Payer's patches of the Gut-associated lymphoreticular tissue.

Limitations:

Main drawback of these polymers is their non specific interaction with cells and plasma proteins, leading to accumulation in non target cells causing limitations in practical drug formulations. Hence, surface modified nanoparticles have been developed to control their interactions. PEG coated (sterically stabilised) nanoparticles can avoid sequestration by the Mononucleur Phagocyte system (MPS) and hence show increased circulation time in the body.

Biodegradable and biocompatible polymers such as poly (lactide) (PLA), poly (ε-caprolactone) (PCL) , poly (β-benzyl L-aspartate) (PLBA) , and poly (γ-benzyl L-glutamate) (PLBG) have been commonly used for the core material of micelles while PEO and PEG are used as hydrophilic blocks. Studies on polymeric micelles comprised of PEO as hydrophilic block and PCL, PLA, PLBA, PLBG as hydrophobic block have been carried out by many groups. PLGA has been successful as a biodegradable polymer because it undergoes hydrolysis in the body to produce the original monomers, lactic acid and glycolic acid. These two monomers under normal physiological conditions, are by-products of various metabolic pathways in the body. PLGA is a common choice in the production of a variety of biomedical devices such as: grafts, sutures, implants, prosthetic devices, micro and nanoparticles. As an example, a commercially available drug delivery device using PLGA is Lupron Depot® for the treatment of advanced prostate cancer.

Polycaprolactones (PCL)

Poly(ε-caprolactone) (PCL) obtained by ring opening polymerisation of ε- caprolactone was first reported by Pitt et al. for the controlled release of steroids and narcotic antagonists as well as to deliver opthalmic agents. PCL, aliphatic polyester has been intensively investigated as a biomedical material. It demonstrates a low melting point (57°C) and a low glass-transition temperature (−62°C).

Degradation: Under physiological conditions, PCL can be degraded by microorganisms as well as by hydrolysis . Under certain circumstances, it is possible to enzymatically degrade crosslinked PCL (termed enzymatic surface erosion).

Properties: Low molecular-weight fragments of PCL are also reportedly absorbed by macrophages intracellularly. The rate of biodegradation for PCL is slower than other

biodegradable materials thus making it suitable for design of long term implantable systems. Another interesting property of PCL is its propensity to form compatible blends with a wide variety of polymers.

Example : cyclosporine encapsulation within Polycaprolactone.

Poly (alkylcyanoacrylates)

Poly (alkylcyanoacrylate)s have been used as tissue adhesives in surgery since these are well tolerated in vivo. Unlike PLA and PGA, here only the side chains are biodegradable and not the backbone. Their delayed degradation characteristics thus do not generate an acidic environment during drug release. The production of NPs by mechanically polymerizing the dispersed methyl or ethyl cyanoacrylate in aqueous acidic medium without irradiation or an initiator in the presence of polysorbate-20 as a surfactant.

Poly (ortho-esters) (POE)

Poly (orthoesters) is another important group of hydrophobic polymer with drug delivery applications and are synthesised by the addition of polyols to diketene acetals. POEs possess acid sensitive orthoester linkages that undergo rapid hydrolysis at physiological pH and an even faster rate in an acidic pH. Therefore, incorporation of a small amount of acidic excipients may help to control the hydrolysis rate. On the other hand, incorporation of basic excipients stabilises the bulk of the matrix but facilitates erosion at the surface. The polymers conjugated with N-hydroxysuccimide were hydrolyzed in a biphasic mode, with a fast initial phase occurring in the first few hours, followed by a slower phase in the next few days. These ionomers represent a novel class of biomaterials with readily controllable physical and chemical attributes for tissue engineering.

Polyanhydrides (PA)

Polyanhydrides are hydrophobic and contain water sensitive linkages that may undergo hydrolytic bond cleavage to generate water-soluble degradation products. Surface erosion takes place due to water sensitive linkages. The majority of Polyanhydrides studied are based on sebacic acid (SA), p- (carboxyphenoxy) propane (CPP) and p-(carboxyphenoxy) hexane (CPH) The Sebacic acid component of biodegradable PAs is utilised as a surface eroding drug delivery device. A wide variety of drug and proteins have been incorporated into PAs and their modified forms e.g. poly (anhydride-esters), poly (anhydride-imides) etc. and their potential release characteristics have been evaluated.

Polyamides

Polyamides form another important class of polymers particularly as drug delivery matrices. Polyamides with a structural resemblance to polypeptides are used as matrices for the transport of drugs. Examples include different types of poly (amino acids) such as poly (L-glutamic acid), poly (aspartic acid) are derived from the corresponding natural amino acids. Nakanishi and co-workers have developed a polymeric micelle carrier system consisting of PEG-conjugated doxorubicin: poly (aspartic acid) for the transport of doxorubicin. This carrier system has a highly hydrophobic inner core, and therefore, it can also entrap a useful amount of doxorubicin in addition to the conjugated doxorubicin. It circulated in the blood for a long-time and evaded RES uptake due to the hydrophilic polyethylene glycol outer layer. It was effectively accumulated in the tumour tissue by the EPR effect. The entrapped Doxorubicin was released from the inner core by diffusion and expressed stronger activity than free Doxorubicin against all the tumour lines tested.

Table 1: List of some condensation polymers

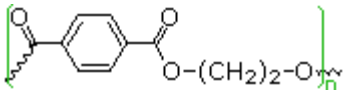
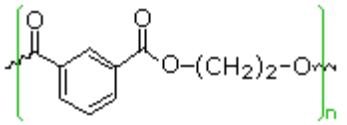
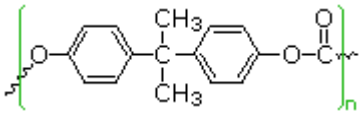
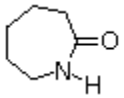
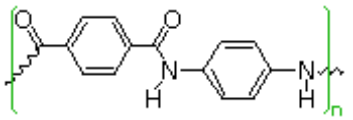
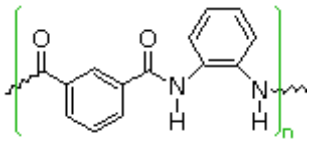
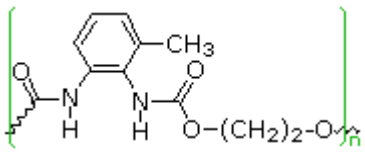
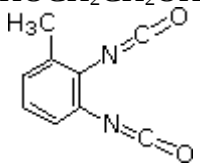
Formula	Type	Components
~[CO(CH$_2$)$_4$CO-OCH$_2$CH$_2$O]$_n$~	Polyester	HO$_2$C-(CH$_2$)$_4$-CO$_2$H HO-CH$_2$CH$_2$-OH
	polyester Dacron Mylar	para HO$_2$C-C$_6$H$_4$-CO$_2$H HO-CH$_2$CH$_2$-OH
	Polyester	meta HO$_2$C-C$_6$H$_4$-CO$_2$H HO-CH$_2$CH$_2$-OH
	polycarbonate Lexan	(HO-C$_6$H$_4$-)$_2$C(CH$_3$)$_2$ (Bisphenol A) X$_2$C=O (X = OCH$_3$ or Cl)
~[CO(CH$_2$)$_4$CO-NH(CH$_2$)$_6$NH]$_n$~	polyamide Nylon 66	HO$_2$C-(CH$_2$)$_4$-CO$_2$H H$_2$N-(CH$_2$)$_6$-NH$_2$
~[CO(CH$_2$)$_5$NH]$_n$~	polyamide Nylon 6 Perlon	
	polyamide Kevlar	para HO$_2$C-C$_6$H$_4$-CO$_2$H para H$_2$N-C$_6$H$_4$-NH$_2$
	polyamide Nomex	meta HO$_2$C-C$_6$H$_4$-CO$_2$H meta H$_2$N-C$_6$H$_4$-NH$_2$
	polyurethane Spandex	HOCH$_2$CH$_2$OH 

Table 2: Environmentally sensitive polymers for drug delivery

Stimulus	Hydrogel	Mechanism
pH	Acidic or basic hydrogel	Change in pH — swelling — release of drug
Ionic strength	Ionic hydrogel	Change in ionic strength — change in concentration of ions inside gel — change in swelling — release of drug
Chemical species	Hydrogel containing electron-accepting groups	Electron-donating compounds — formation of charge/transfer complex — change in swelling — release of drug
Enzyme-substrate	Hydrogel containing immobilized enzymes	Substrate present — enzymatic conversion — product changes swelling of gel — release of drug
Magnetic	Magnetic particles dispersed in alginate microshperes	Applied magnetic field — change in pores in gel — change in swelling — release of drug
Thermal	Thermoresponsive hrydrogel poly(N-isopro-pylacrylamide)	Change in temperature — change in polymer-polymer and water-polymer interactions — change in swelling — release of drug
Electrical	Polyelectrolyte hydrogel	Applied electric field — membrane charging — electrophoresis of charged drug — change in swelling — release of drug
Ultrasound irradiation	Ethylene-vinyl alcohol hydrogel	Ultrasound irradiation — temperature increase — release of drug

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