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Review Article

Shrewd natural and synthetic biodegradable polymers for targeted sustain and controlled release formulation

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Abstract

In recent years there has been increase in interest of biodegradable polymers. Biodegradability depends not only on the origin of the polymer but also on its chemical structure and the environmental degrading conditions. Two classes of biodegradable polymers can be distinguished: synthetic or natural polymers. There are polymers produced from feedstocks derived either from petroleum resources (non renewable resources) or from biological resources (renewable resources).Natural and synthetic Biodegradable polymers are extensively used for the development of various dosage forms. Biodegradable polymers are generally hydrophilic in nature and have limited swelling characteristic in acidic ph. Linear polysaccharides remains intact in stomach and small intestine so they can be use for controlled release formulation and the bacteria of human colon degrades them and thus make them potentially useful in colon targeted drug delivery systems. Various drug delivery systems have been designed that deliver the drug quantitatively to the colon and then trigger the release of drug. This review will cover different types of polymers which can be used in formulation of sustain, controlled and colon targeted drug delivery systems.

Key words : Biodegradable polymers, sustain delivery, colon targeted delivery, controlled delivery.

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1. Introduction

Biodegradation takes place through the action of enzymes and/or chemical deterioration associated with living organisms. This event occurs in two steps. The first one is the fragmentation of the polymers into lower molecular mass species by means of either abiotic reactions, i.e. oxidation, photo degradation or hydrolysis, or biotic reactions, i.e. degradations by microorganisms. This is followed by bioassimilation of the polymer fragments by microorganisms and their mineralization. The oral route is considered to be most convenient for administration of drugs to patients. Oral administration of conventional dosage forms normally dissolves in the stomach fluid or intestinal fluid and absorb from these regions of the git depends upon the physicochemical properties of the drug. It is a serious drawback in conditions where localized delivery of the drugs in the colon

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is required to be protected from the hostile environment of upper git. Targeted delivery of drugs to the colon has attracted much interest recently for local treatment of a variety of colonic diseases (ulcerative colitis, chron's disease, carcinomas and infections) as well as systemic absorption of protein and peptides.[1,2] To produce sustained and controlled release formulation of an oral liquid and solid dosage form could be successfully augmented substantially through a strategy of liquid in-situ floating gel system, various type of coating and matrix preparation can be formulated by using biodegradable polymers.[3,4]

Need for Biodegradable polymers:

- The surgical removal of a non-biodegradable foreign materials is required to remove when it remain in the body for indefinite time period which causes toxicity problem.
- While diffusion controlled release is an excellent means of achieving controlled drug delivery, it is limited by the polymer permeability and the characteristics of a drug increase, its diffusion coefficient decrease.
- There is no need for a second surgery for removal of Polymers.
- Avoid stress shielding.
- Offer tremendous potential as the basis for controlled drug delivery.

Advantage of biodegradable polymers:

- It provides a drug at a constant controlled rate owes a prescribed period of time.
- The polymer carrier would degrade into nontoxic, absorbable subunits which would be subsequently metabolized.
- The system would be biocompatible would not exhibit dose dumping at any time and polymer would retain its characteristics untill after depletion of the drug.
- Degradable system eliminates the necessity for surgical removal of implanted device following depletion of a drug.
- They are broken down into biologically acceptable molecules that are metabolized and removed from the body via normal metabolic pathways.

Disadvantage of biodegradable polymers:

- Sometimes the degradable polymers exhibit substantial dose dumping at some point following implantations.
- A “burst effect” or high initial drug release soon after administration is typical of most system.
- Degradable systems which are administered by injection of a particulate form are non-retrievable

Natural Biodegradable Polymers:

Natural gums and their derivatives are used widely in pharmaceutical dosage forms, their use as biodegradable polymeric materials to deliver bioactive agents has been hampered by the synthetic materials. These natural polysaccharides do hold advantages over the synthetic polymers, generally because they are nontoxic, less expensive, and freely available. Natural gums can also be modified to have tailor-made materials for drug delivery systems and thus can compete with the synthetic biodegradable excipients available in the market

Guar gum

Guar gum is derived from the seeds of the *cyomopsis tetragonolobus* (fam. Leguminosae). Chemically, guar gum is a polysaccharide composed of the sugars galactose and mannose. The backbone is a linear chain of β 1,4-linked mannose residues to which galactose residues are

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1,6-linked at every second mannose, forming short side-branches fig1. Guar gum is hydrophilic in nature and swells in cold water forming viscous colloidal dispersions or sols.[6] This gelling property retards release of the drug from the dosage form as well as it is susceptible to degradation in the colonic environment. So it can be used for controlled release and targeted drug delivery systems due to its drug release retarding property and susceptibility to microbial degradation in large intestine.

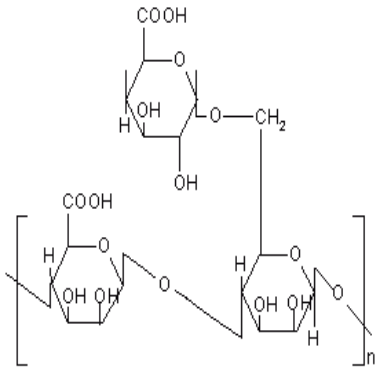


Figure 1: chemical structure of guar gum.

Homogenized and diluted feces from human source were incubated with the guar gum to investigate the degradation of polysaccharide by intestinal microflora. It produced a rapid decrease in viscosity and fall in ph while no such results were observed when it was incubated with autoclaved fecal homogenates.[8] Wong *et al* [9] studied the dissolution of dexamethasone and budesonide from guar gum-based formulations using reciprocating cylinder dissolution apparatus (USP dissolution apparatus iii) and observed that the drug release in simulated colonic fluid was markedly increased at galactomannanase concentrations >0.01 mg/ml. Krishnaiah *et al* [10] Performed a gamma scintigraphic study on guar gum matrix tablet using technetium-99m-dtpa as a tracer, in human volunteers. The scintigraphs showed that some amount of tracer present on the surface of the tablets was released in stomach and small intestine and the bulk of the tracer present in the tablet mass was delivered to the colon. These results indicated that guar gum, in the form of directly compressed matrix tablets, is a potential carrier for colon-specific drug delivery. Vinay wamorkar *et al* [11]have studied sustain release formulation and evaluation of stomach specific *in-situ* gel of metoclopramide by using guar gum.

Rosin

Rosin is a natural non-volatile resinous mass obtained from *pinu palustris* miller and other species such as *pinus linnae*. Some rosin biopolymers are reported to have excellent biocompatibility and biodegradation features.[12] It primarily contains resin tricyclic diterpene carboxylic acids (abietic and pimaric) figure-2 and a few amounts of nonacidic components. Rosin contains approximately 90% rosin acids. The rosin acids are monocarboxylic acids and have a typical molecular formula $c_{20}h_{30}o_2$.

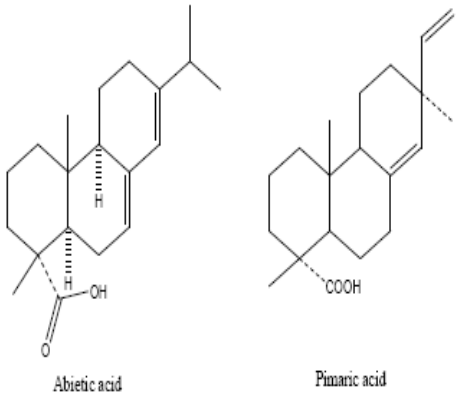


Figure 2: Tricyclic diterpene carboxylic acids (abietic and pimaric)

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Excipient	Test	Pharmacopeia
Guar gum	Ph, microbial contamination, apparent viscosity, loss On drying, ash, galactomannans, organic volatile impurities	USP, pheur
Sodium alginate	Microbial limit, appearance of solution, loss on drying, ash, heavy metals	USP, pheur
Xanthan gum	Ph, viscosity, microbial limits, loss on drying, ash, heavy metals, organic volatile impurities	USP, pheur
Gellan gum	Ph, microbial limit, loss on drying, moisture content, specific gravity, solubility, bulk density	USP
Lecithin	Water, arsenic, lead, acid value, heavy metals	USP
Carrageenan	Solubility, viscosity, loss on drying, ash value	USP
Gelatin	Isoelectric point, microbial limit, residue on ignition, loss on drying, total ash, jelly strength	USP, JP, pheur

Table 1.pharmacopoeial specifications for natural biodegradable polymers

Natural polymers	Modification technique	Application	Reference
Sesbania gum	Chemical modification of *sesbania*gum with tartaric acid for a sustained release formulation and chemical modification of gum with acetone: chloroform mixture for gelling agent	Sustained release Formulation, gelling agent	65
Guar gum	Chemical modification of guar gum with glutaraldehyde for colonic delivery, chemical	Sustained release Formulation, colonic delivery, film coating,	66
Tamarind Powder	Chemical modification of tamarind powder using epichlorohydrin for a sustainedrelease formulation and partial degradation of β galactosidase for rectal drug delivery	Sustained release Formulation, rectal drug delivery	67
Pectins	Chemical modification of pectin with acetyl chloride in ethanol for modified drug delivery, chemical modification with ethanolamine for hydrogels and chemical modification of pectin for colonic drug delivery.	Modified drug Delivery. Hydrogels, colonic drug delivery	68
Okra fruit (pods) of *hibiscus esculentus*	Chemical modification with acrylamide synthesis	Controlled drug Delivery	69

Table2. Examples of some modified natural biodegradable polymers with their applications

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Esters of rosin are reported to have good film forming properties and can be used for enteric coating and delayed Release of drugs. Rosin and rosin-based polymers have drug delivery applications achieving sustained/controlled Release profiles. [13,14] One of the good inherent properties exhibited by rosin biomaterials is their film forming ability, utilise in the development of film based drug delivery systems and dosage forms, therefore rosins can be used in the development of transdermal drug delivery rosin and its derivatives have been used in the formulation of different pharmaceutical preparations [15] Rosin a natural biomass, is used as a matrix forming polymer for tablet formulations. Rosin-glycerol esters have been reported as micro-encapsulating materials for controlled drug delivery.[16] Drug release rate are physicochemical properties of drugs, which depend on degradation rate of polymers, and the morphology and size of microparticles. The biodegradable property of rosin makes it possible to implant them into the body without the need of subsequent removal by the surgical operation. Drug formulated with these polymers can be released in a controlled manner, by which the drug concentration in the target site is maintained within the therapeutic range. The release rates of the drugs from biodegradable polymers can be controlled by a number of factors, such as biodegradation kinetics of the polymers [17,18] physicochemical properties of the polymers and drugs thermodynamic compatibility between the polymers and drugs, and the shape of the devices. S.lakshmana *et al* [19]have formulated and evaluated oral sustain release of diltiazem hcl by using rosin as a matrix forming material. Thus it can be concluded that rosin and rosin-based polymers have drug delivery applications achieving sustained/controlled release profiles.[20] Lakshmana prabu s *et al* [21] studied sustained release microspheres of rosin containing aceclofenac.

Pectin

Pectin is a polysaccharide consists of -1, 4 d-galacturonic acid and 1, 2 d-rhamnose with d-galactose and d-arabinose side chains figure 3. A novel colonic drug delivery system based on the polysaccharide pectin has been investigated. *In vitro* experiments demonstrated that high methoxy pectin, when applied as a compression coat, proved capable of protecting a core tablet during conditions stimulating gastrointestinal environment and was susceptible to enzymatic attack.

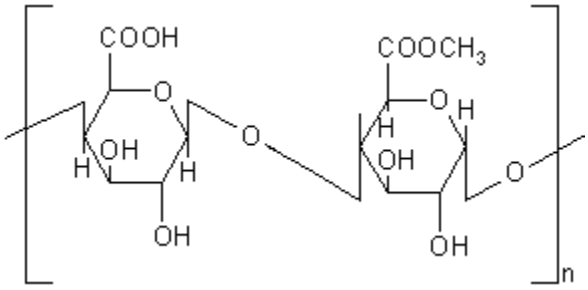


Figure 3: -1, 4 d-galacturonic acid and 1, 2 d-rhamnose with d-galactose and d-arabinose side chains

In vivo gamma scintigraphic studies confirmed the *in vitro* findings. In all the volunteers, the pectin-coated tablets disintegrated in the colon indicating that site-specificity had been achieved and illustrating the potential of a colonic drug delivery system utilizing pectin. However, in the *in vivo* conditions, a coat of considerable thickness was required to protect the drug core. This necessitates the development of such derivatives of pectin, which were less water-soluble but were

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having the capability to be degraded by the colonic microflora. Calcium pectinate, the insoluble salt of pectin was used for colon targeted drug delivery of indomethacin by rubeinstein et al [22] ashford et al [23] prepared matrix tablets of a model compound sodium fluorescein and assessed *in vitro* , the potential of several pectin formulations as colon targeted drug delivery systems was studied. The potential of an orally administered *in situ* gelling pectin formulation for the sustained delivery of paracetamol has been studied by wataru k *et al* [24]

Xanthum gum

Xanthan gum is a high molecular weight extra cellular polysaccharide produced by the fermentation of the gram-negative bacterium xanthomonas campestris.The primary structure of this naturally produced cellulose derivative contains a cellulosic backbone (β-d-glucose residues) and a trisaccharide side chain of β-d-mannose-β-d-glucuronicacid-α-d-mannose attached with alternate glucose residues of the main chain fig4. The anionic character of this polymer is due to the presence of both glucuronicacid and pyruvic acid groups in the side chain.[25] The formulation and characterization of 5-flourouracil matrix tablets by using xanthum and pectin gum was studied for colon targeted drug delivery by yaswanth allamneni et al [27]

Okra gum

Okra gum, obtained from the fruit of hibiscus esculentus, it is a polysaccharide contain d-galactose, l-rhamnose and l-galacturonic acid. Dhana lakshmi B [28] have done formulation and evaluation of aceclofenac matrix tablet using abelmoschus esculentus mucilage as a polymer for sustain release and In other study okra gum was evaluated as controlled release agent in comparison

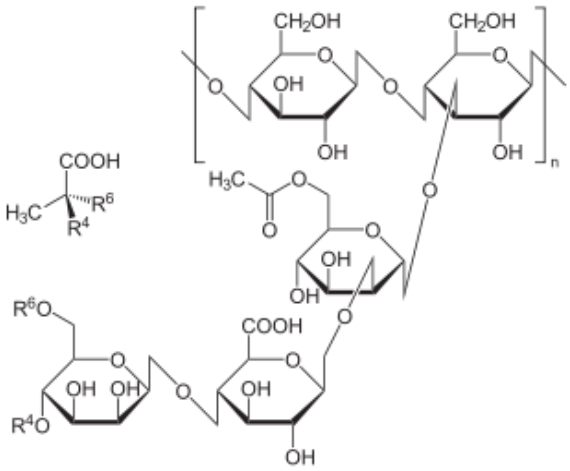


Figure 4: Chemical structure of Xanthum gum

with NACMC and HPMC, using paracetamol as model drug. Okra gum matrix provided controlled release of paracetamol for more than 6hrs. Finally he concluded from result that okra gum may be useful for hydrophilic matrixing agent in sustain and controlled release formulation. Ilango K B et al [29] Colon targeted tablet formulation was developed using okra polysaccharide as a microbially triggered material and also as the carrier. Okra polysaccharide was isolated from *Abelmuschus esculentus* and used for tablet formulation with Ibuprofen as model drug. These observations drive to conclude that the okra polysaccharide under investigation has the potential to carry the drug almost intact to the intended site i.e. Colon where it undergoes degradation due to the presence of anaerobic microbes. Hence it can be use for targeted drug delivery.

Chitosan

Chitosan is a high molecular weight polycationic polysaccharide derived from naturally occurring chitin by alkaline deacetylation. Chemically, it is a poly (N-glucosamine) Figure 5. Chitosan has favourable biological properties such as nontoxicity, biocompatibility and biodegradability. Similar to other polysaccharides it also undergoes

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degradation by the action of colonic microflora and hence poses its candidature for colon targeted drug delivery.[30]

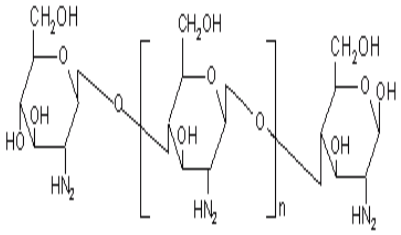


Figure 5: Chemical structure of chitosan

The naturally occurring polymer chitosan was reacted separately with succinic and phthalic anhydrides. The resulting semisynthetic polymers were assessed as potential matrices for colon-specific, orally administered drug delivery using sodium diclofenac as the dispersed model drug. The prepared matrices were incorporated into tablets, evaluated in vitro which resisted dissolution under acidic conditions. On the other hand, improved drug release profiles were observed under basic conditions that suggest the suitability of the prepared matrices in colon-specific, orally administered drug delivery system.[31] Tozaki et al [32] evaluated colon-specific insulin delivery using chitosan capsules. It was found that these were stable in the stomach and small intestine but degraded by micro-organism in rat caecal contents upon entering into the colon proving their utility as carriers for colon targeted drug delivery of peptide and nonpeptide drugs. A. Polk et al [33] have formulated and evaluated polymeric controlled release protein delivery system and investigated with albumin as a model drug. The polysaccharide chitosan was reacted with sodium alginate in the presence of calcium chloride to form microcapsules with a polyelectrolyte complex membrane. Capsules produced with high molecular weight chitosan and a combination of high and low molecular weight chitosan gave the best results for reducing elution of albumin in the first 4 h and increasing elution in the following 20 h.

Alginate:

Sodium alginate is a salt of Alginic acid - a linear block copolymer polysaccharide consisting of β-D-mannuronic acid and α-L-glucuronic acid residues joined by 1,4-glycosidic linkages.[34] Aqueous solutions of alginates form firm gels on addition of di- and trivalent metal ions. The results indicated that the alginates form compact structures when the ionic radii of the cation are lower. Sodium alginate has been employed in the preparation of gels for the delivery of biomolecules such as drugs, peptides and proteins.[35] Moin K. Modasiya et al [36] have design and evaluate in situ gelling system for oral sustained release drug delivery of Famotidine, which was selected as a model drug due to its short biological half-life (2-3 hrs). In-vitro release study revealed that drug released from the insitu gel followed non-fickian diffusion. Hence sodium alginate can be use for sustain release formulation. Alginic acid can be chosen as a vehicle for controlled release ophthalmic formulations, since it exhibits favorable biological properties such as biodegradability and nontoxicity. A prolonged precorneal residence of formulations containing alginic acid was looked for, not only based on its ability to gel in the eye, but also because of its mucoadhesive properties.[37] Liu Xing et al [38] have studied alginate for novel formulation of oral administration using coated calcium alginate gel beads-entrapped liposome and bee venom peptide as a model drug has been investigated for colon-specific drug delivery in vitro. Drug release studies under conditions mimicking stomach to colon transit have shown that the drug

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was protected from being released completely in the physiological environment of the stomach and small intestine.

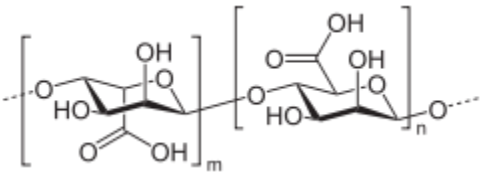


Figure 6: Chemical structure of alginate

Gellan Gum:

Gellan gum (commercially available as Gelrite™ or Kelcogel™) is an anionic deacetylated exocellular polysaccharide secreted by Pseudomonas elodea with a tetrasaccharide repeating unit of one α-L-rhamnose, one β-D-glucuronic acid and two β-D-glucuronic acid residues. Chemical structure of the polysaccharide has a tetrasaccharide repeat unit consisting of two glucose residues, one glucuronic acid residue, and one rhamnose residue. These are linked together to give a tetrasaccharide repeat unit.[39] Hetangi Rathod et al [40] have done development, evaluation, and optimization of gellan gum based in situ gel using ambroxol-HCl as a model drug and it was concluded that gellan gum is excellent of sustain release formulation.

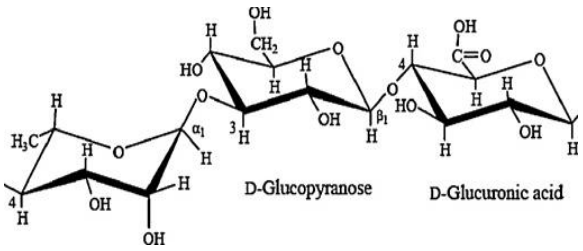


Figure 7: Chemical structure of gellan gum

Synthetic Biodegradable Polymers Derived from Petroleum Resources

Synthetic polymers are popular choice mainly for parenteral preparations. The trend in drug delivery technology has been towards biodegradable polymers, requiring no follow up surgical removal, once the drug supply is depleted. Aliphatic polyesters such as poly (lactic acid), poly (glycolic acid), poly (lactide- coglycolide), poly (decalactone), poly ε-caprolactone have been the subject of the most extensive recent investigations.[41] various other polymers like triblock polymer systems composed of poly(d,l-lactide)-block-poly(ethyleneglycol)-block-poly(dl-lactide), blends of lowmolecular weight poly(d,l-lactide) and poly(ε-caprolactone) are also in use. These polymers are mainly used for the injectable formulations. The feasibility of lactide/glycolide polymers as excipients for the controlled release of bioactive agents is well proven. These materials have been subjected to extensive animal and human trials without evidence of any harmful side effects. When properly prepared under GMP conditions from purified monomers, the polymers exhibit no evidence of inflammatory response or other adverse effects upon implantation.[42]

Aliphatic polyesters

This class is the most extensively studied class of biodegradable polymers, because of their important diversity and its synthetic versatility. Various routes leading to the development of synthetic polyesters exist and have been recently reviewed.[43] Polycondensation of difunctional monomers preferentially yields low molecular weight polymers. Ring opening polymerization is preferred when high molecular polymers are desired. Most biodegradable polyesters are prepared via ring opening polymerization of six or seven membered lactone.[44] Aliphatic polyesters can be classified into two types according to the bonding of the constituent monomers. The first class consists of the polyhydroxyalkanoates. These are

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polymers synthesized from hydroxyacids, HO-R-COOH. Examples are poly(glycolic acid) or poly(lactic acid). Poly(alkene dicarboxylate)s represent the second class. They are prepared by polycondensation of diols and dicarboxylic acids. Examples are poly(butylene succinate) and poly(ethylene succinate).

Polyglycolide (PGA)

PGA is the simplest linear aliphatic polyester. It is prepared by ring opening polymerization of a cyclic lactone, glycolide. It is highly crystalline, with a crystallinity of 45-55% and thus is not soluble in most organic solvents. It has a high melting point (220-225 °C) and a glass transition temperature of 35-40 °C. PGA has excellent mechanical properties. Nevertheless its biomedical applications are limited by its low solubility and its high rate of degradation yielding acidic products. Consequently, copolymers of glycolide with caprolactone, lactide or trimethylene carbonate have been prepared for medical devices [45,46]

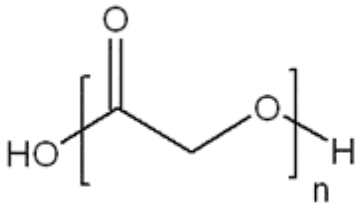


Figure 8 : General structure of PGA

Polylactide (PLA)

PLA is usually obtained from polycondensation of D- or L-lactic acid or from ring opening polymerization of lactide, a cyclic dimer of lactic acid. Two optical forms exist: D-lactide and L-lactide. The natural isomer is L-lactide and the synthetic blend is DL-lactide. Other different synthetic methods have also available.[47] Regulation of the physical properties and biodegradability of PLA can be achieved by employing a hydroxy acids comonomer component or by racemization of D- and L- isomers. Regulation of the physical properties and biodegradability of PLA can be achieved by employing a hydroxy acids comonomer component or by racemization of D- and L-isomers.[48] A semi-crystalline polymer (PLLA) (crystallinity about 37%) is obtained from L-lactide whereas poly(DL-lactide) (PDLLA) is an amorphous polymer[49]. Their mechanical properties are different as are their degradation times.[50] PLA has disadvantages of brittleness and poor thermal stability. PLA can be plasticized to improve the chain mobility and to favor its crystallization. Plasticization is realized with oligomeric acid, citrate ester or low molecular polyethylene glycol [51]. Different companies commercialize PLA with various ratios of D/L lactide and trade names and suppliers of different grades of PLA are listed in Table 03. R Dinarvand [52] have done the review studied for Polylactide-co-glycolide nanoparticles for controlled delivery of anticancer agents.

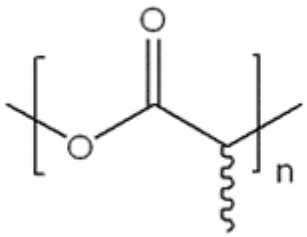


Figure 9: General structure of PLA

Poly(Lactide-Co-Glycolide)

PLGA degrades through hydrolysis of its ester linkages in the presence of water. It has been shown that the time required for the degradation of PLGA is related to the ratio of monomers used in its production: the higher the content of glycolide units, the lower the time required for degradation. An exception to this rule is copolymer with 50:50 ratio of

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PLGA Type	Drug	Method	Form/Size	Degradation Time	References
50:50	bone morphogenetic protein	double-emulsion–solventextraction technique	microspheres	least 42 days *in vitro*	72
85:15	paclitaxel	electrospinning technique	implants in the form of microfiber discs and sheets	over 80 days *in vitro* with a small initial burst	73
85:15	vascular endothelial growth factor	a double emulsion/solvent extraction technique	microspheres	30 days	74
75:25	vincristine sulfate and quercetin	using a probe sonicator	nanoparticles/nanocomposites	-	75
50:50; 70:30; 75:25	vincristine sulfate and quercetin	modified version of an o/w single-emulsion solvent evaporation process	nanoparticles	70% of drugs released from nanoparticles after 24 h	76
50:50	folic acid	physicochemical solvent/nonsolvent method	nanoparticles	over 30 days *in vitro*	77

Table 4. Delivery Systems of PLGA Nano/Microparticles Obtained in Various Labs in 2008

Trade name	Company	Country
NatureWorks	Cargill Dow	USA
Galacid	Galactic	Belgium
Lacea	Mitsui Chem	Japan
Lacty	Shimadzu	Japan
Heplon	Chronopol	USA
CPLA	Dainippon Ink Chem	Japan
Eco plastic	Toyota	Japan
Treofan	Treofan	Netherlands
PDLA	Purac	Netherlands
Ecoloju	Mitsubishi	Japan
Biomer L	Biomer	Germany

Table 3: Trade names and suppliers of PLA

monomers, which undergoes faster degradation (about two months) in both *in vitro* and *in vivo conditions*.[55-58] Miller *et al.* have shown that PLGA 50:50 is the fastest degrading composition, with the degradation rate being decreased when either lactide orglycolide content of the copolymer was increased.[59] PLGA can be synthesized by a polycondensation reaction, orvia ring-opening polymerization of cyclic diesters Figure 10. Ring-opening polymerization is currently the preferred method for the synthesis for PLGA and PLA due to shorter reaction times and higher monomer conversion

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rates.[60-63] Yan et al showed[64] that the cytotoxicity of a PLGA-poloxamer188 nanoparticle blend containing docetaxel against MCF-7 TAX30 cells was higher than that of the free drug, indicating that poloxamer188 could enhance the ability of PLGA nanoparticles to overcome multidrug resistance. A docetaxel-loaded PLGA-poloxamer188 nanoparticle formulation has been developed to overcome multidrug resistance in a docetaxel-resistant human breast cancer cell line.

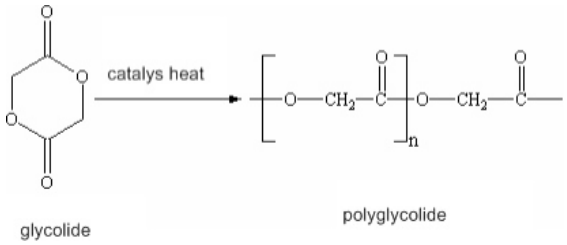


Figure 10: synthesized of PLGA by a polycondensation reaction

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