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TECHNICAL ADVANCEMENT IN BIODEGRADABLE POLYMERS AND THEIR RECENT PATENTS

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ABSTRACT: The plethora of drug therapies and types of drugs demand different formulations, fabrications conditions and release kinetics. No single polymer can satisfy all the requirements. Therefore, there have been tremendous advances in area of biodegradable copolymers over the last 30 years. This article reviews current research on biodegradable polymers, focusing their potential as drug carries. The major classes of polymers are briefly discussed with regard to synthesis, properties and biodegradability, and known degradation modes and products are indicated based on studies reported in the literature. A vast majority of biodegradable polymers studied belongs to the polyester family, which includes polyglycolides and polylactides. Other degradable polymers such as polyorthoesters, polyanhydrides and polyphosphazenes are also discussed and their advantages and disadvantages are summarized.

INTRODUCTION: Polymers first developed in search for biodegradable suture materials have been proven to be useful and successful for long-term drug delivery applications. Biodegradable polymers are highly desirable in these situations because they degrade in the body to biologically inert and compatible molecules. By incorporating drugs in biodegradable polymers, dosage forms that release the drug over a prolong length of time can be prepared in variety of shapes and sizes. No surgical procedures are needed after completion of dosage regime since the remaining polymer will degrade and get cleared by the body. As a result, biodegradable polymers offer a novel approach for developing sustained release drug delivery systems that are simple and convenient to patient [1, 2, 3].

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Current scenario: 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. 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 [4, 5]. These technical developments in drug delivery approaches improve human health. Use of polymeric material in novel drug delivery approaches has attracted the scientists [6].

Need for Biodegradable polymers:

- It was recognized that the surgical removal of a drug depleted delivery system was difficult yet leaving non-biodegradable

foreign materials in the body for an indefinite time period caused 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 [10].

Advantage of biodegradable polymers:

- It provides drug at a constant controlled rate over 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 until 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.
- Ability to change surface chemically and physically.
- Ability to immobilize cells or biomolecules within them or on the surface (Drug Eluting Stent).

Disadvantage:-

- 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
- Presence of substances that may be issued in the body [monomers (toxic), catalysts, additives] after degradation
- Ease of water and biomolecules absorption from surrounding
- Low mechanical properties
- In some cases, difficult sterilization

Biodegradable Polymers as Drug Carriers: A polymer is a large molecule composed of many smaller units called monomers that are bonded together. In addition to eliminating the necessity of removal, the five key advantages that polymeric drug delivery products can offer are; localized delivery of drug, sustained delivery of drug, stabilization of the drug, release rate which is less dependent of the drug properties and steadier release rate with time. In diffusion controlled systems the release rate typically declines with time [7, 8]. On the other hand, a biodegradable system may yield a constant release even with a simple monolithic device if matrix degradation can compensate for this decline, perhaps with an increase of drug permeability [9].

Selection Criteria of Polymer:

- Should have regulatory approval.
- Simple mechanism of degradation yielding no toxic monomer residue.
- Properties like bulk hydrophilicity, morphology, structure, and extent of drug polymer interactions can be manipulated by adding copolymer in different ratio.

Drug release Mechanism from Polymer: Biodegradation and erosion is the main mechanism of drug release. Degradation is characterized by a loss of molecular weight and initiates polymer erosion. Polymer degradation accompanied by change in the properties like tensile strength, color, shape etc. of a polymer or polymer based product under the influence of one or more environmental factors such as heat, light or chemicals [11, 12]. The polymer degradation can be classified as Chemical erosion and Physical erosion [13].

Physical Erosion: The physical erosion mechanisms can be characterized as heterogeneous or homogeneous. In heterogeneous erosion, also called as surface erosion, the polymer erodes only at the surface, and maintains its physical integrity as it degrades. Most polymers undergo homogeneous erosion, means the hydrolysis occurs at even rate throughout the polymeric matrix. Generally these polymers tend to be more hydrophilic than those exhibiting surface erosion. As a result, water penetrates the polymeric matrix and increases the rate of diffusion. In homogeneous erosion, there is loss of integrity of the polymer matrix.

Chemical Erosion: Many mechanisms exist for chemical degradation such as mechanism I, II or III. In mechanism I the water-soluble macromolecules that are cross-linked are prone for degradation to form three-dimensional network. In Mechanism II, the dissolution of water-insoluble macromolecules with side groups that are converted to water-soluble polymers occurs as a result of ionization, protonation or hydrolysis of the groups. Materials displaying type II erosion include cellulose acetate derivatives and partially esterified copolymers of maleic anhydride. These polymers become soluble by ionization of carboxylic group.

Mechanism III is followed by the insoluble polymers with labile bonds. Hydrolysis of labile bonds causes scission of the polymer backbone, thereby forming low molecular weight, water-soluble molecules. Polymers undergoing type III erosion include poly (lactic acid), poly (glycolic acid) and their copolymers, poly (ortho esters), polyamides, poly (alkyl-2-cyanoacrylates) and polyanhydrides.

Generally the three mechanisms are not mutually exclusive; combinations of them can occur during drug delivery process [2].

Factor affecting biodegradable polymers:

Polymer Morphology: The morphology of a polymeric material (i.e. amorphousness and semicrystallinity) plays a critical role in enzymatic and non-enzymatic degradation processes. It is now known that degradation of semicrystalline polymers in aqueous media occurs in two stages. The first stage consists of diffusion into amorphous regions with random hydrolytic scission of ester bonds. The second stage starts when most of the amorphous regions are degraded.

The hydrolytic attack then progresses from the edge towards the center of crystallites. This phenomenon was first observed by Fischer *et al* who investigated the structure of solution grown crystals of PLA stereo polymers by means of chemical reaction. Amorphous polymers are preferable for sustained drug delivery systems because they usually yield a smooth surface and a uniform structure, which retains the drug for long periods of time. In contrast, a semicrystalline polymer generally leads to rough surfaces and porous structures, which are suitable for sustained delivery of drugs.

Molar Mass and Molar Mass Distribution: Molar Mass and Molar Mass distribution is important factors in the polymer degradation and drug release process because of the autocatalytic character of the aliphatic polyester hydrolysis. There are three types of degradation profile according to the molar mass, namely parabolic, linear and s-type. The parabolic type observed for 1500Da can be explained by the release of the soluble fraction present within the initial oligomers, whereas s-type 3500Da reflects a lag time due to higher molar mass [14].

From the data available, one can conclude that the lower the molar mass, the faster the degradation rate, In agreement with the presence of the more carboxylic acid catalyzing groups.

Size and Porosity: The size of the polymer samples has also been regarded as important factor for the degradation of aliphatic polyesters.

The degradation rate is much faster in pellets than in fibers. Lam *et al* observed a faster degradation of nonporous films as compared with porous films [15]. The micro particles exhibited a more prolonged drug release profile, indicating that the fusion process may have substantial advantages for thermo stable drugs requiring long term release. In hollow fibers the release was found to be dependent on the membrane wall and zero order was achieved for as long as 6 months [16].

Drug load and Drug Polymer interaction: Many authors report that the drug release rate increased with increasing drug load [17, 18, 19, 20, 21, 22, 23]. This can be assigned to morphology and distribution of drugs within the polymer matrix. With small loads the release is slow because drug molecules are dissolved or molecularly dispersed within the matrix. In contrast with high loads, drug crystals can be formed. The initial burst generally leads to channels and pores that facilitate diffusion later on. Therefore the degradation of the PLA polymers in the presence of basic drugs appeared rather complex because of the contribution of a number of parameters (base catalysis, neutralization of carboxyl end group's porosity, dimensions of devices, drug load and drug morphology). None of these factors can be considered separately if one wants to understand the effect of basic drug on properties of drug delivery system.

pH and Ionic strength: No major difference was observed between and acidic media. The effects of pH and ionic strength were interpreted in terms of electric potential distribution at the polymer solution interface. Degradation was also found affected by salt concentration in buffer solutions, suggesting that the cleavage of polymer ester bond was accelerated by conversion of the acidic degradation products into neutral salts [23]. Therefore one can easily conclude that the alkaline and strong acidic media accelerate the polymer degradation. The difference between the slightly acidic and physiological media, however, is much less pronounced due to autocatalysis by carboxyl end groups. Nevertheless one can assume that for degradation controlled release, drug release should be enhanced. In the case of diffusion controlled release, one should take into account the solubility of the drug in the external medium [24] (**Table 1**).

TABLE 1: PRODUCTS WITH DIFFERENT BIODEGRADABLE POLYMERS

Application	Trade Name	Composition	Manufacturer	Reference
Sutures	Vicryl	PLLA (8%)-co-PGA (92%)	Ethicon	46
	Polysorb	PGA-LPLA	U.S. Surgical	47
Interference screws	Sysorb	DLPLA	Synox	48
	Endofix	PGA-TMC or LPLA	Acufex	49
	Anthrex	LPLA	Anthrex	50
	Phusiline	LPLA-DLPLA	Phusis	51
Suture Anchor	Biostatak	LPLA	Zimmer	52
	Bankart tack	SR-LPLA	Bionx Implants	48
	SmartAnchor –D	SR-LPLA L	Bionx Implants	48
	SmartAnchor-L	R-LPLA	Bionx Implants	48
	Phantom Suture	LPLA	DuPuy	48
	Biologically quiet	85/15 DLPLG	Instrument makar	48
	Panalok	82/18 LPLG	Surgical dynamics	48
Dental	Drilac	DLPLA	THM Biomedical AHP	
Angioplastic plug	Angioseal	PGA-DLPLA	Bionx	
Screw	SmartScrew	LPLA	Bionx	48
Tack	SmartTack	LPLA	Lorenz	48
Plates, Mesh, Screws	LactoSorb	PGA-LPLA		48
Ligating clips, bone pins and rods	Biofix	LPLA or PGA	BIonx	48
Guided Tissue	Resor-Pin	LPLA-DLPLA	Geistlich	48
	Lactosorb	LPLA	Davis and Geck	48
	Antisorb	DLPLA	Procordia	56
	Resolut	PGA-DLPLA	W.L.Gore	55
	Guidor	DLPLA	Procordia	54
Drug Delivery Products	Lupron Depot	PLA/PLGA	TAP	53
	Zoladex	PLA/PLGA	AstraZeneca	26

Different Technologies and Products based on Biodegradable Polymers:

Decapeptyl®: Decapeptyl SR injection contains the active ingredient triptorelin acetate, which is a type of medicine known as a Gonadorelin (LHRH) analogue. It acts on the pituitary gland in the brain. The pituitary gland produces and stores various hormones, including the sex hormones, luteinizing hormone (LH) and follicle-stimulating hormone (FSH). In men, LH released from the pituitary gland causes the testicles to produce testosterone. FSH and testosterone cause the production of sperm by the testicles. In women, FSH and LH cause the production of estrogen by the ovaries and help control the menstrual cycle. The amount of LH and FSH released from the pituitary gland is controlled by another hormone, called gonaderelin (LHRH). Gonadorelin acts on LHRH receptors in the pituitary gland, causing the release of LH and FSH and hence the subsequent production of testosterone in men and estrogen in women.

Adriamycin®: Doxorubicin is an antineoplastic in the anthracycline class. General properties of drugs in this class include: interaction with DNA in a variety of different ways including intercalation (squeezing between the base pairs), DNA strand breakage and inhibition with the enzyme topoisomerase II. Most of these compounds have been isolated from natural sources and antibiotics. However, they lack the specificity of the antimicrobial antibiotics and thus produce significant toxicity.

The anthracyclines are among the most important antitumor drugs available. Doxorubicin is widely used for the treatment of several solid tumors while daunorubicin and idarubicin are used exclusively for the treatment of leukemia. Doxorubicin may also inhibit polymerase activity, affect regulation of gene expression, and produce free radical damage to DNA. Doxorubicin possesses an antitumor effect against a wide spectrum of tumors, either grafted or spontaneous. The anthracyclines are cell cycle-nonspecific.

Zoladex®:-Zoladex® (AstraZeneca) is supplied as a sterile, biodegradable product containing goserelin acetate equivalent to 3.6 mg of goserelin [25].

Zoladex® is designed for subcutaneous injection with continuous release over a 28 d period. Goserelin acetate is dispersed in a matrix of D, L-lactic and glycolic acids copolymer (13.3-14.3 mg/dose) containing less than 2.5% acetic acid. The encapsulated drug is released by a combination of diffusion and erosion-controlled mechanisms. However, because the delivery device is a monolithic, heterogeneous hydrolysis is thought to be the predominant erosion process.

Lupron depot®: The first FDA-cleared PLGA product was the Lupron Depot® drug-delivery system (TAP Pharmaceutical Inc.). Lupron Depot® is a microsphere formulation based on the biodegradable polymers of polylactic acid (PLA) and poly(lactic/glycolic acid) [25]. The double-emulsion process is used to manufacture Lupron Depot®. The primary emulsion consists of leuprorelin acetate in an aqueous solution containing gelatin dispersed in a solution of PLG in methylene chloride. The water-in-oil emulsion is then emulsified in a solution of poly(vinyl alcohol) (surfactant and stabilizer). The microspheres are formed by evaporation of the methylene chloride, which is the continuous phase of the primary emulsion.

Gliadel® wafer: Gliadel® Wafer is a white, dime-sized wafer made up of a biocompatible polymer that contains the cancer chemotherapeutic drug, carmustine (BCNU). On removal of a high-grade malignant glioma, up to eight Gliadel Wafers are implanted in the cavity where the tumor resided.[25] Once implanted, the Gliadel Wafers slowly dissolve, releasing high concentrations of BCNU into the tumor site targeting microscopic tumor cells that sometimes remain after surgery. Gliadel wafer was the first new treatment of this kind or brain cancer introduced in over 20 years. In the field of local delivery, carmustine-loaded Gliadel wafer (Guilford Pharmaceuticals, Baltimore, MD) fabricated from poly(carboxyphenoxypropane: sebacic acid) proved very promising in clinical trials for the treatment of malignant glioma, increasing both survival and safety. BCNU-loaded Gliadel wafer provides localized delivery of chemotherapy directly to the site of the tumor (as an adjunct therapy) and is the only FDA approved brain cancer treatment capable of doing so [26].

Alzamer® depot technology: Alzamer® technology offers a non-aqueous polymer solution for sustained delivery of small molecules and biopharmaceuticals for periods of weeks to months, both locally and systemically. Protein stability is maintained in Alzamer® depot formulations by isolating the drug in a solid particle. This particle is suspended in the non-aqueous polymer solution to prevent premature exposure to water. Processing of both the gel and protein particles is simple, incorporating standard lyophilization and aseptic blending techniques. No reconstitution or additional mixing is required.

Atrigel *in situ* implant system: This system can be used for both parenteral and site-specific drug delivery. It contains a biodegradable polymer dissolved in a biocompatible carrier. When the liquid polymer system is placed in the body using conventional needles and syringes, it solidifies upon contact with aqueous body fluids to form a solid implant. If a drug is incorporated into the polymer solution, it gets entrapped within the polymer matrix as it solidifies, and is slowly released as the polymer biodegrades. The Atrigel® system is protected by more than 140 patents in the United States and the rest of the world.

Both the basic technologies as well as process improvements are covered in these patents. Seven products have already been approved by the FDA using the Atrigel technology like Eligard® and the Atridox. The poly(DL-lactide), lactide/glycolide copolymers, and lactide/caprolactone copolymers are most often used because of their degradation characteristics and their approval by the FDA. The solvents employed in the Atrigel system to dissolve the polymers range from the more hydrophilic solvents, such as N-methyl-2-pyrrolidone (NMP), polyethylene glycol, tetraglycol and glycol furol, to the more hydrophobic solvents, such as triacetin, ethyl acetate and benzyl benzoate [26] (**Table 2**).

TABLE 1: RECENT PATENTS PUBLISHED ON BIODEGRADABLE POLYMERS

Publication No.	Applicant	Title	References
WO 2001060335 A2	3M innovative Properties Company	Delivery systems using preformed biodegradable polymer compositions and methods	27
US 20130041311 A1	The Trustees Of Columbia University In The City Of New York	Methods, devices, and systems for on-demand ultrasound-triggered drug delivery	28
US20130023830 A1	Sanofi-Aventis Deutschland Gmbh	Drug delivery device with biodegradable plastic components	29
US20130084322 A1	Tim Wu	Drug-impregnated biodegradable stent and methods of making the same	30
US8414642	Advanced Cardiovascular Systems, Inc.	Biodegradable stent of a polyorthoester polymer or a polyanhydride polymer	31
US8377499 B2	Abbott Cardiovascular Systems Inc.	Methods of forming Poly(ester amide)-based drug delivery systems with controlled release rate and morphology	32
EP0863745 B1	Macromed Inc.	Thermosensitive biodegradable polymers based on poly(ether-ester) block copolymers	33
EP1257257 A2	3M Innovative Properties Company	Delivery systems using preformed biodegradable polymer compositions and methods	34
WO2012115806 A1	University of Iowa Research Foundation	New biodegradable polymers with sulfenamide bonds for drug delivery applications	35
US8303625 B2	Helmholtz-Zentrum Geesthacht Zentrum Fuer Material- Und Kuestenforschung Gmbh	Biodegradable shape memory polymeric sutures	36
WO2012006359 A1	Novartis Ag	Delivery of self-replicating rna using biodegradable polymer particles	37
WO2012141660 A1	Ústav Polymérov Sav	Biologically degradable polymeric composition with high deformability	38
US8343472 B2	Polynovo Biomaterials Pty Limited	Biodegradable polyurethane/urea compositions	39
EP2473542 A1	Co2starch Pty Ltd	Polymer/thermoplastic starch compositions	40

US20130018111 A1	Agency For Science, Technology And Research	Biodegradable and biocompatible shape memory polymers	41
WO2013057748 A1	Colplast S.R.L.	Trimmer line comprising a biodegradable polymeric material and a relative biodegradable polymeric material	42
WO2013007872 A1	Stora Enso Oyj	A heat-sealable biodegradable packaging material, a package or a container made thereof, and use of a resin in extrusion coating	43
US8299172 B2	Saginaw Valley State University	Biodegradable plastics	44
US8389614 B2	Cereplast, Inc.	Biodegradable nanopolymer compositions and biodegradable articles made thereof	45

CONCLUSION: New tailor-made polymers with desirable functional groups are being created by researchers who foresee their use not only for innovative drug delivery systems but also as potential linings for artificial organs, substrates for cell growth, chemical reactors, agents in drug targeting and immunology testing. Biodegradable polymers also have vast applications in scaffolds: Tissue engineering. We expect that, in future even more than today, device designers and physicians will have a wealth of products using biodegradable polymers that will help speedy patient recovery and eliminate follow-up surgeries.

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