Jordan Journal of Pharmaceutical Sciences, Volume 11, No. 3, 2018

Technical Insight into Biodegradable Polymers Used in Implants

Rafeef Masadeh,[1] Rana Obaidat,[1] Mo'tasem Alsmadi,[1] Bashar Altaani,[1]*

Mai Khanfar,[1] Rawda Alshyab,[1] Mohammed Qaoud1[1]

[1] Department of Pharmaceutical Technology, Faculty of Pharmacy,
Jordan University of Science and Technolog, Jordan.

ABSTRACT

The development of the biodegradable implant drug delivery system (BIDDS) is described in this review, and technical details about polymers are highlighted specifically for researchers working in the field. The discovery of biodegradable polymers in the beginning of the 1960s was the first step to develop biodegradable implants. The advantages of biodegradable implants over non-biodegradable implants motivated further research. A detailed summary on the polymers used in BIDDS is provided, as well as their therapeutic applications in chemotherapy, vascular disease, ocular drug delivery and the development of vaccinations, among others. Moreover, improvements in the formulation to increase efficacy and patient adherence and to minimize adverse effects are reviewed. Finally, the challenges and future of BIDDSs are discussed.

Keywords: polymers

1. INTRODUCTION

The need for a new dosage form emerged due to the limitations of oral and parenteral formulations, including their short duration of action, higher dosing frequency, low patient adherence and poor therapeutic outcomes. Many approaches have been used to address these disadvantages and achieve the controlled release of drugs after parenteral administration, including the use of suspensions, viscous formulations, complex formulations, oil preparations and subcutaneous implantation of drug pellets (i.e., implants).[1-3] Implants, in particular, overcame many of the limitations, improving patient adherence and resulting in optimal pharmaceutical care outcomes.[4-6]

An implant is a dosage form that may be inserted subcutaneously for a systemic effect, or in certain body cavities for a local effect.[4,5] For local action, implants are administered via intra-cerebrospinal, intraventricular, intra-articular, and intraocular routes.[4] The advantages of implants may be summarized as follows[7]:

1- Automatic drug release, which may increase patient adherence.
2- Decreased frequency of dosing.
3- Decreased incidence of adverse effects by controlled drug release and/or by localized drug action.
4- Decreased amount of drug required due to surpassing of drug degradation pathways.
5- Improved drug bioavailability, especially for drugs that undergo extensive first-pass metabolism after oral administration.
6- Decreased need for intravenous drug administration, resulting in reduced hospital stays for the treatment of chronic diseases.
7- Immediate cessation of medication release by implant removal in response to allergic or adverse effects.

On the other hand, implants have a number of limitations, such as the following[7]:

1- Minor surgery required for implant insertion and

* Rafeef Khalid Massadeh
Received on 18/12/2016 and Accepted for Publication on 20/12/2017.

 © 2018 DAR Publishers/The University of Jordan. All Rights Reserved.

oftentimes removal, which may decrease patient adherence.

2- Specialized skills required for optimal implantation.
3- High cost-benefit ratio.
4- Higher complexity of the fabrication process and approval pathway for implant dosage forms, which also makes them more expensive to manufacture.
5- Pain and discomfort, depending on the implantation site.

Additionally, the potential for fibrous encapsulation or the foreign body reaction are major disadvantages of implants, which may also result in undesirable release of drug from the implant.[8] However, these problems may be minimized by decreasing the diameter of the biodegradable fibers to less than 5µm.[9] This may cause a difference in stress distribution at the tissue-fiber interface and in the hydrophobicity of the implant material used.[9]

BRIEF HISTORY OF IMPLANTS

The 1960s was a revolutionary decade for implantable drug delivery systems. During this time, Deanspy and Parkes started the concept of and research into implantable drug delivery systems. They compressed pellets of crystalline estrone, inserted them subcutaneously into castrated male chickens and described the effects of these implants. They observed the appearance of new feathers as they appeared for three months.[7] Folkman and Long (1964) later used a silicon rubber-based polymeric membrane to control the release of drug and prolong systemic drug administration.[10]

An implant needs to possess the following qualities: safety, efficacy, stability, low toxicity, high biocompatibility, lack of carcinogenicity, compatibility of carrier and drug (to avoid burst release or shutdown), and patient and physician acceptance. All of these requirements meant that progress on the development of implant formulations was initially slow. However, when the silicone-based device Norplant® (levonorgestrel implant) (**Figure 1)** was approved by the U.S. Food and Drug Administration (FDA) in 1990, the number of published articles and commercial products increased.[7] Further research resulted in an increased variety of new implantation techniques, sites of administration and implant designs that improved the safety, efficiency, and relevance of implanted drugs.

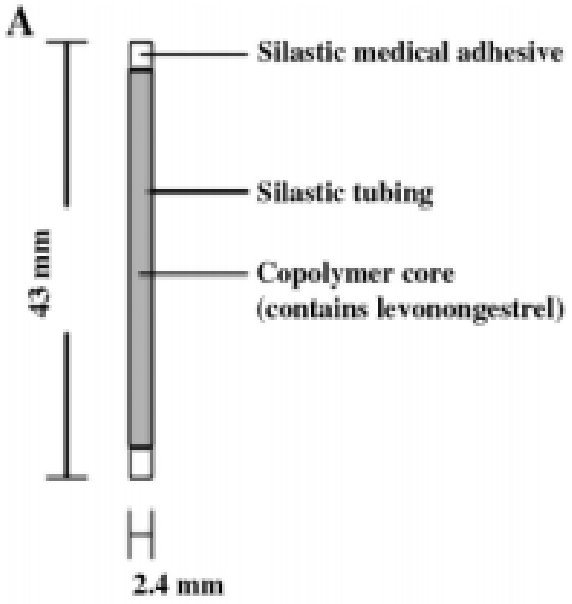

Figure 1: Norplant (levonorgestrel) implant capsule, the first implant device approved by the U.S. Food and Drug Administration (FDA), with actual size shown (source: Population Council, 1990)[7]

TYPES OF IMPLANTS

Drug implants may be divided into two main categories: non-biodegradable and biodegradable[7]. They are mainly composed of polymeric material that forms the implant skeleton through which the drug material is dispersed. Excipients may be added to improve the structure of the formed skeleton and to increase the biocompatibility and stability of the implant[7]. The focus of this review is on biodegradable implants; however, non-biodegradable implants will be discussed briefly.

1- Non-biodegradable implants

The polymers in non-biodegradable implants maintain their structure throughout the treatment period, without being affected by surrounding biological fluids. After a surgical procedure to implant the non-biodegradable device, its removal requires a second, minor surgical procedure. Polyethylene vinyl acetate (PEVA) is an example of a non-biodegradable polymer using a matrix. Examples of drugs that have been formulated as non-biodegradable implants include the following:

A-Ocusert® (pilocarpine): Ocusert was an implant inserted into the conjunctival cul-de-sac of the eye. It was used to treat glaucoma by delivering pilocarpine. The outer shell was composed of PEVA, which controlled the rate of drug release. The drug was released within one week.[11]

B-(Progesterone): In this formulation, progesterone is dispersed in silicon oil which is coated with PEVA as a rate-controlling reservoir. Used for contraception, the implant continuously releases the drug over the course of one year.[11]

C-(Levonorgestrel): This is an example of a drug formulation for intrauterine administration. The implant releases levonorgestrel for more than five years.[7]

2- Biodegradable implants

Most of the recent research on implants has been directed at creating biodegradable implants, especially for drugs used for a short period of time. Unlike with non-biodegradable implants, a second surgery to remove the implant is not needed, because the implanted polymer degrades in the body by its interaction with body fluids, resulting in the normal healing process. The design of biodegradable implants is a major challenge. However, due to their complexity and the high cost and low availability of polymers with desired *in vivo* degradation kinetics, a series of tests should be done prior to approving a new biodegradable implant. These include determining the mechanism and kinetics of its *in vivo* degradation and the resulting degradation species. The age of the patient and changes in the body's anatomy and physiology due to disease may cause variability in the outcomes of biodegradable implants.[7]

Of note here is that there is specific terminology used when discussing biodegradable implants. As terms are often used incorrectly and interchangeably, some of them are discussed here. "Bio" implies that a process occurs *in vivo* and/or within the biological media of a living organism. "Degradation" means that a chemical and/or physical reaction is occurring, which leads to the loss of the original physical and chemical properties (desirability is influenced by the degradation kinetics). "Erosion" describes the removal and transport of material which leads to the progressive loss of the material. Plenty losses in physical property kinetics lead to bulk and surface erosion mechanisms. "Corrosion" is an electrochemical breakdown of metal or metal alloy. "Resorption" is a process of material degradation followed by assimilation. Finally, "absorption" is the process in which a material permeates through another one. These terms are used to describe biodegradable implants and their polymers.

Polymers used in biodegradable implants should possess certain criteria such as the following:

1- Ability to be metabolized in body fluids and excreted by a physiological pathway.
2- Ease of fabrication.
3- Ability to break down into nontoxic, non-cytotoxic (i.e., not mutagenic) materials.
4- Not causing any inflammation after application by injection or insertion.[12-14]

Additionally, the end products after breakdown of the

biodegradable polymers should be considered. Carbon dioxide, water and/or minerals should be the final products of aerobic degradation of biodegradable polymers.[15] Therefore, lactic acid, glycolic acid and their copolymers are considered ideal biodegradable polymers.[16] They are the most commonly used among the aliphatic polyesters. Since the early 1970s, much attention has been paid to these materials, since after eight years of research; a suture was fabricated by melt extrusion of polyglycolic acid.[17] The polymers were later used as excipients, then finally as implants. Other well-known biodegradable polymers include polyanhydrides, poly (ortho esters), and polyphosphoesters.[18]

Parenteral biodegradable polymers may be categorized as synthetic or natural, depending on their origin. Natural polymers are considered biocompatible and biodegradable.[19] For example, alginate, chitosan, collagen and gelatin have been incorporated into parenteral controlled-release systems as drug carriers.[20,21]

Polyamides and polyamino acids are other materials that may be used. Nylon 6 has been investigated in a huge biomedical application and found to be recommended in fabricating inert implants.[22] Poly(alkyl-2-cyanoacrylates) are also used to fabricate biodegradable dosage forms. "Instant glues" and tissue adhesives are fabricated from 2-cyanoacrylate monomers.[23]

Biodegradable polymers have been incorporated into numerous implants for different therapeutic applications, such as the treatment of cancer and relief of pain associated with cancer.[16] Specific biodegradable polymers will be discussed in further detail later in this article.

TYPES OF IMPLANT SYSTEMS

1- Implantable pump system

Implantable pump systems have many advantages, including avoidance of the first-pass effect by bypassing the gastrointestinal tract (GIT); improving patient adherence, especially for drugs that require repeated administrations; having release rates that are better than in diffusion-limited systems; and having more localized action by easily inserting the pump at the desired site of action.

Implantable pump systems may be divided into two types: osmotic pumps and infusion pumps. If the pump allows the diffusion of water across a semipermeable membrane due to a high concentration of solute in the opposing side of the membrane, it is called an osmotic pump system. It may be inserted subcutaneously or into other sites. It may be coated with titanium alloy or a biocompatible polymer. The DUROS® is an example of an implanted osmotic pump system; it is used to deliver the gonadotropin releasing hormone agonist leuprolide for the treatment of prostate cancer.

An infusion pump, on the other hand, is made of two parts: the cannula and the pump. Whereas the cannula portion of the delivery system is implanted, the pump is worn outside the body. It is usually used to deliver minute amounts of insulin as a subcutaneous infusion in the treatment of diabetes.[7]

2- Micro- and nano-fabricated implantable drug delivery systems

Microtechnology and nanotechnology (using microliter- or nanoliter-sized reservoirs) have attracted the attention of researchers over the past decade.[25,26] These types of systems are still under development. They consist of a chip of silicon wafer to which tiny microliter-sized reservoirs are attached and filled with a drug or multiple drugs. A film of gold or other material is used to cover these reservoirs, which are electronically addressable on the chip. After implantation of the chip, dissolution of the film is induced electrochemically by applying a voltage to the foil of an individual reservoir, causing drug release from that reservoir. It is possible to have pulsatile, patterned, or controlled release of a single or multiple drugs.[24]

3- Insertable drug delivery systems

Many body sites may be used for placement of insertable drug delivery systems. It may cause a local effect (e.g., an ocular insert delivering drug into the eye) or a systemic effect (e.g., a subcutaneous insert delivering

drug into the blood stream). Transurethral, vaginal and intrauterine routes are also sites for implantation, using these drug delivery systems.[16]

Models of drug release from insertable drug delivery systems

- The Higuchi model was the first model presented in the 1960s to describe the kinetics of drug delivery and other aspects of system function.[27]
- The extended Higuchi model was used by Paul and McSpadden.[28]

Polymers used in biodegradable implants

1- Polylactic acid (PLA), polyglycolic acid (PGA), poly(D,L-lactic-co-glycolic acid) (PLGA) and their derivatives:

Implants fabricated from these polymers do not elicit chronic foreign body reactions[29] after insertion, and, as they are biodegradable, there is no need to remove the device after complete drug release.[30,31] PLGA is the most commonly used polymer to fabricate biodegradable implants due to the simplicity of controlling its degradation half-life by changing the ratio of lactide to glycolide (**Figure 2**). Its degradation takes weeks to years, depending on the lactide to glycolide ratio and the composition of the lactide stereoisomeric mixture.[32] PLGA-based polymers are relatively easy to construct into various body forms, such as rods, screws, plates and pins. Other factors that may affect drug release are molecular weight, degree of crystallinity [33], surface area of the device, and the loaded drug percentage.[34]

In general, drug release from the implant occurs in three stages (**Figure 3)**:

1- During burst release, the drug begins to be released from the implant surface, and there is high drug release in a short period of time.
2- Diffusion and chain scission are controlled by the solubility of the drug in the surrounding media. The hydrolysis-induced cleavage of polymer chains increases drug release due to the increased porosity and surface area available for drug diffusion.
3- Eventually, biodegradation and mass loss occurs. Mass loss starts at the central core of implant, causing burst release in some delivery systems.[30,35-37]

The following are examples of biodegradable implants using the polymers PLGA, PLA, PGA and/or their derivatives:

A) PLGA copolymers have been used to deliver macromolecules (e.g., hydrochlorothiazide, theophylline) and macromolecules (e.g. myoglobin, cytochrome C). A solution or suspension formula with minor viscosity may be injected subcutaneously using a 22- or 23-gauge needle. The formula is injected under the skin, and once it comes in contact with the aqueous fluid, it is transformed to a gel matrix similar to that of an implant, releasing the drug gradually over weeks to months.

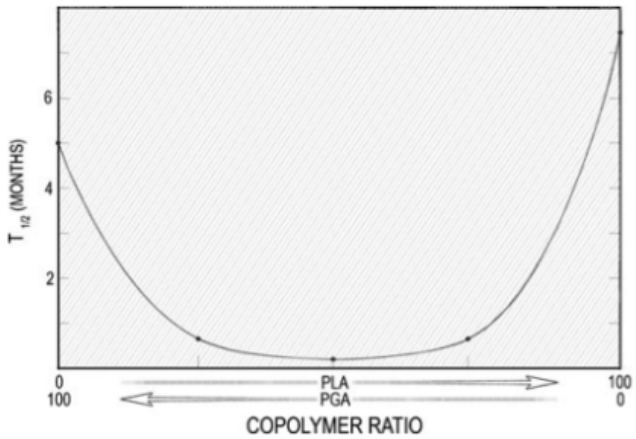

Figure 2: The graph illustrates the relationship between the degradation half-life of PLGA and lactide/glycolide content (31)

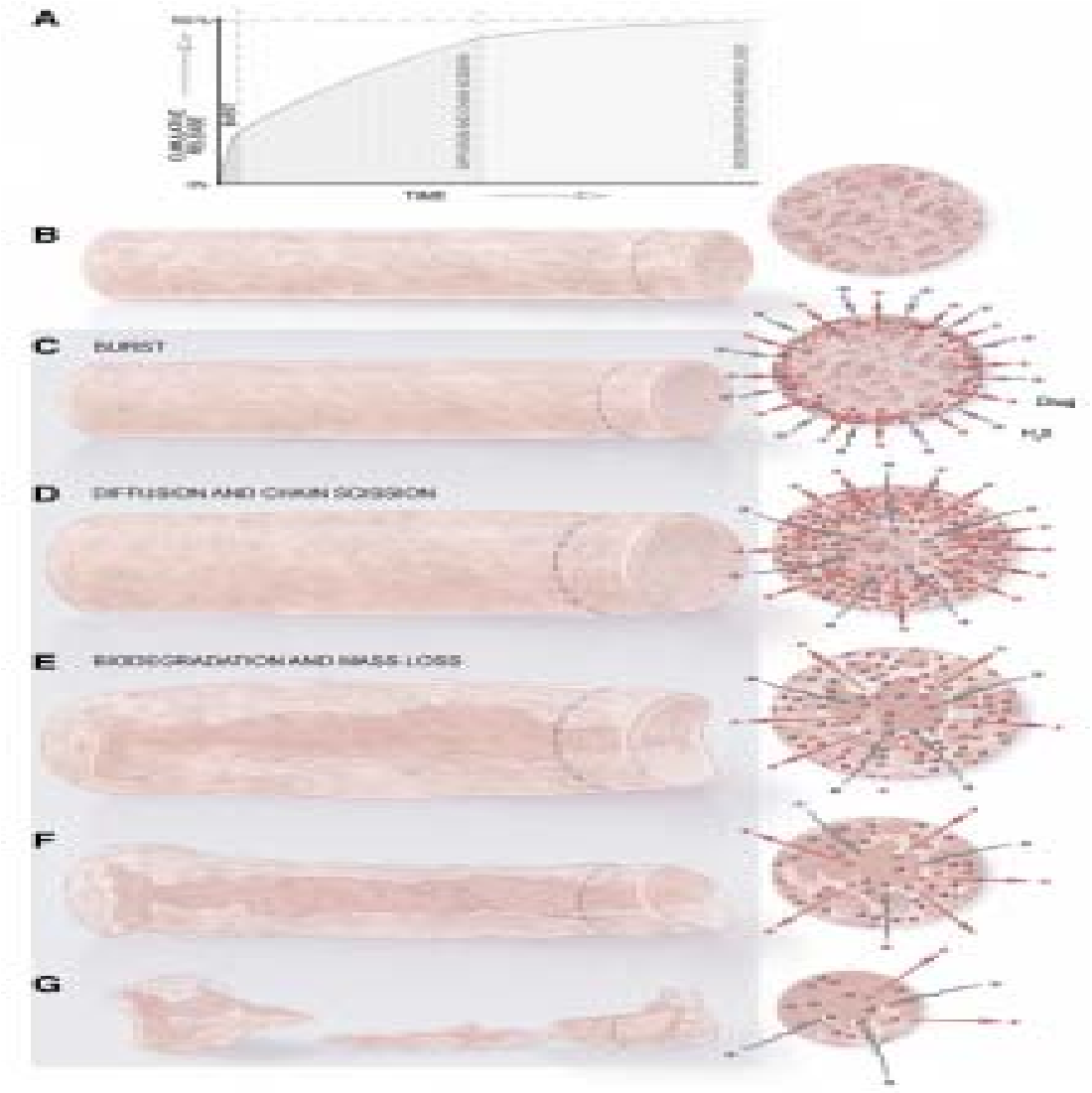

Figure (3): A- the graph shows the cumulative release of drug from PLGA implant at each phase and biodegradation. B- the plant condition prior implantation, its dry and show porous structure of PLGA. C- burst phase. D- diffusion and chain scission. E- biodegradation and mass loss. F- biodegradation continuing lead to change the implant shape. G- implant breakdown to reach the end of biodegradation[(31)

Drug release occurs through a porous network of tortuous channels created by the dissolution of drug in addition to partitioning and diffusion through the matrix. When drug disperses and dissolves, its release rate is faster than if it had only dissolved.

The rate of drug release may be modified as needed by changing the ratio of the copolymer components (e.g., a 50:50 PLGA provides a release over 30 to 40 days). Drug release is also affected by other factors, such as drug physicochemical properties, the way the drug is incorporated into the formulation, and the addition of other excipients.

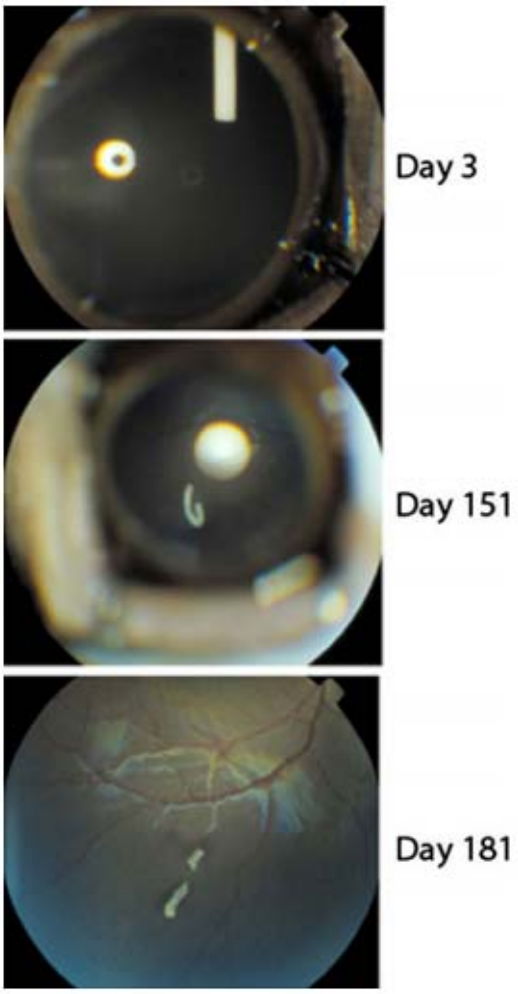

Figure (4): Degradation of OzurdexR in the monkey eye [31]

Limitations of these injectable biodegradable implants include the complexity of the manufacturing process, the instability of drugs caused by heat and the solvents used, and the inability of the human body to terminate therapy by eliminating these microspheres.[38]

B) Zoladex® is another example of a biodegradable implant drug delivery system. It is used as a treatment for prostate cancer and breast cancer. The drug, goserelin acetate, is incorporated into a sterile biodegradable polymer of PLGA. It is presented as a cylinder, preloaded into a single-use syringe, and packed in a light- and moisture-resistant, sealed aluminum pouch. Erosion and diffusion mechanisms usually control drug release from this system.

A 16-G needle is used to inject Zoladex® 3.6mg subcutaneously, and continuous release of goserelin occurs over a period of 28 days. The Zoladex® 10.8mg implant uses a 14-G needle and releases the drug over a period of three months.[39,40] According to the literature, PLGA is biodegraded completely without any potential antigenic adverse effects.[41]

C) Polyglycolide, polylactide, polycaprolactone and their copolymers were incorporated into the design of an

injectable biodegradable implant for naproxen (Tipton *et al.*, 1992) and for doxycycline hyclate (Dunn *et al.*, 1991). By changing the mole ratios of the constituent monomers and molecular weights, the degradation rates were adjusted.[38]

D) Establishing safe and efficacious ocular treatments is challenging due to the specific nature of the eye, poor ophthalmic drug uptake, the frequent lack of specificity to the target tissue, potential systemic adverse effects, and bad adhesion to therapy (**Table 1)**. However, **ocular implant therapy** has solved many of these challenges and provided prolonged therapeutic concentrations at the target ophthalmic tissue, minimizing the need for frequent drug reapplication and improving patient adherence.[32] Hence, many serious complications have been avoided, such as retinal detachment, vitreous hemorrhage, endophthalmitis, cataract formation, and intraocular pressure (IOP) elevation.[42,42]

Table (1): Limitations of ocular drug delivery method [(31)]

Method	Limitations
Topical administration	• Limited uptake
	• Tear dilution/washout
	• Short acting
	• Poor adherence to therapy
Intravitreal injection	• Targeted delivery
	• Invasive/inconvenient/short lasting
	• Adverse events related to injection
Systemic administration	• Limited ocular penetration
	• Systemic toxicity
Nonbiodegradable implants	• Invasive surgery
	• Require removal
	• Adverse events related to implantation or removal surgery

As previously mentioned, synthetic aliphatic polyesters, including polylactic acid (PLA), polyglycolic acid (PGA) and poly(lactic-co-glycolic acid) (PLGA), are the most commonly used for designing biodegradable implants. Various studies on the compatibility and safety of biodegradable implants consisting of PLA or PLGA inserted in various tissues of the eye have found that they are well-tolerated.[37,44-46] Examples of ocular implants utilizing these polymers include the following:

1-Ozurdex®: This is composed of 7mg of

dexamethasone dispersed in a PLGA copolymer (diameter of 0.45mm, length of 6.5mm), and is inserted intravitreally with a 22-G needle. It is used for the treatment of macular edema due to branch retinal vein occlusion (BRVO) or central retinal vein occlusion (CRVO).[47]

2-Ganciclovir: The drug ganciclovir is incorporated into a biodegradable scleral implant to treat cytomegalovirus retinitis. The implant is composed of 25% ganciclovir, and the matrix is composed of the biodegradable polymers poly(D, L-lactide) 7000 and poly(D, L-lactide) 5000, with a blending ratio of 80:20. The implant studied in pigmented rabbit eyes showed effective ganciclovir concentrations for 6 months without significant burst.[48]

3- Triamcinolone: The drug triamcinolone has been incorporated into an implant dosage form to treat postoperative inflammation. The matrix is composed of PLGA (MW: 80,000 Da) loaded with 1,050mg of triamcinolone. This biodegradable drug delivery system (DDS) combined with an artificial intraocular lens (IOL) **(Figures 5 and 6)** proved to be more effective in relieving postoperative inflammation for 84 days and had good ocular biocompatibility.[49]

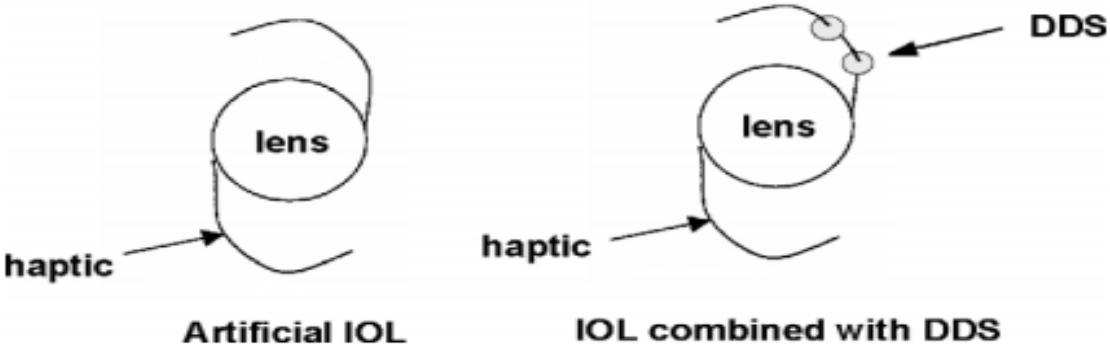

Figure (5): Artificial IOL as implanted during cataract surgery and IOL combined with two drug delivery system, threaded onto an IOL haptic (48)

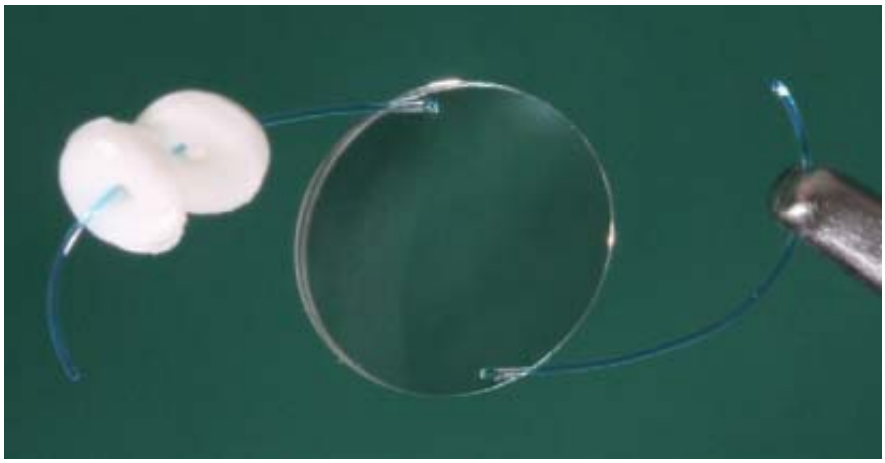

Figure (6): Intraocular lens combined with two DDS (48)

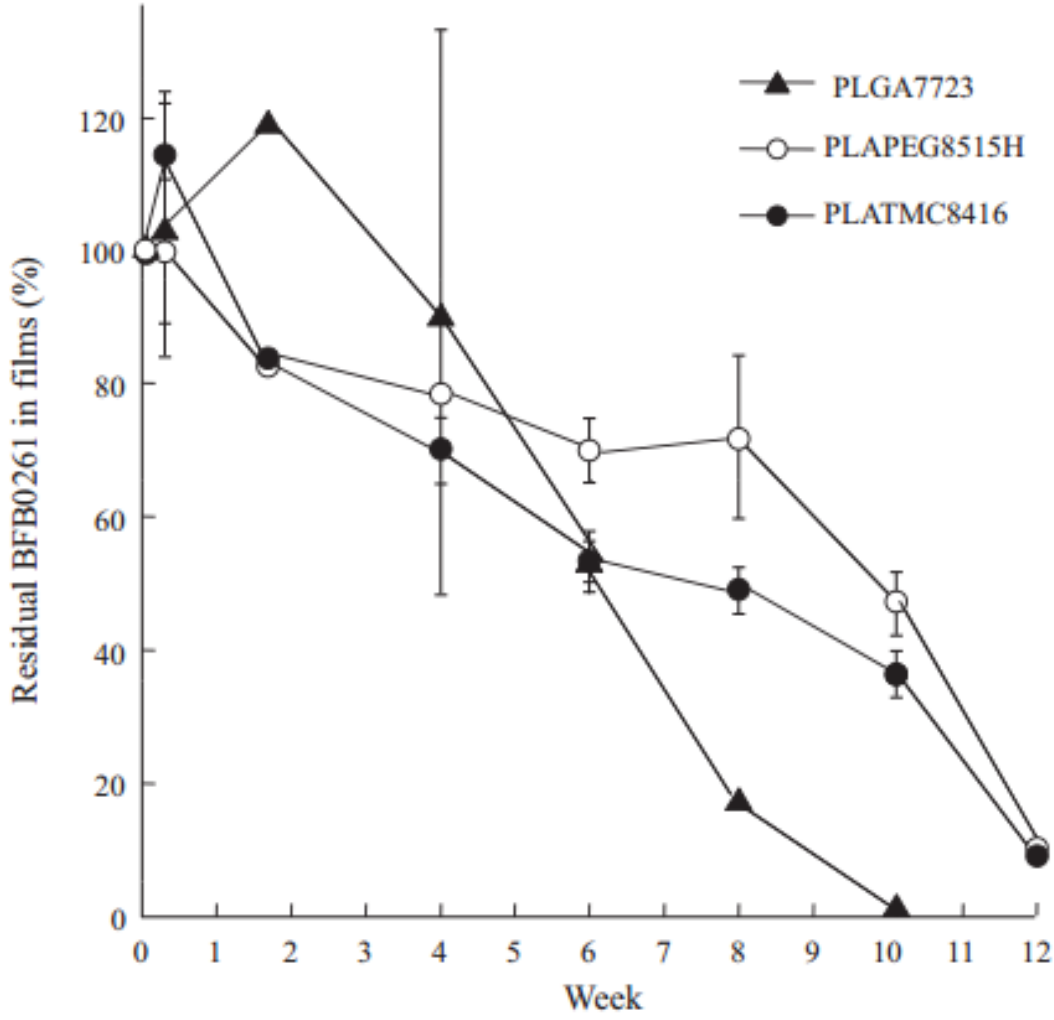

Figure (7): *In-Vivo* BFB0261 release profiles after subcutaneous implantation on rat backs. Film dimension was 10 mm × 25 mm. Films containing 1 mg of BFB0261. Various polymers such as PLGA7723, PLAPEG8515H, and PLATMC8416 were used [(49)]

E) A potent **osteogenic compound BFB0261** (3-ethyl-4-(4-methylisoxazol-5-yl)-5-(methylthio) thiophene-2-carboxamide) for treating bone disorders has been incorporated into a biodegradable implant. Different types of polymers were studied, including PLA100 (MW: 251 kDa), PLAPEG9604H (PLA/PEG ratio: 96:4, MW: 181 kDa), PLAPEG8515H (PLA/PEG ratio: 85:15, MW: 51.5 kDa), PLAPEG8020 (PLA/PEG ratio: 80:20, MW: 33.7 kDa) and PLATMC8416 (PLA/TMC ratio: 84:16, MW: 170 kDa).When the PLAPEG8515H or PLATMC8416 copolymer loaded with BFB0261 was inserted subcutaneously in rat backs, zero-order sustained release and first-order sustained release, respectively, were achieved at the site of administration over 12 weeks (**Figure 7)**. Film fabricated from PLGA, PLA-PEG, or PLA-TMC polymers exhibited tougher and more elastic properties than PLA films alone.[62]

F) A **biodegradable implant for fracture fixation** fabricated from PLGA was developed to replace the conventional metallic implant used in fracture fixation

(**Figure 8**). There was no difference noted in the therapeutic effect in rabbits, and the biodegradable implant was advantageous because the usual surgical procedure to remove the metallic implant was precluded. In addition, the long-term stress protection induced by metallic fixation was avoided with the biodegradable implant. During the therapeutic period, the metallic fixation required 62 days for the bone fracture to heal, while the biodegradable implant required 57 days.[63]

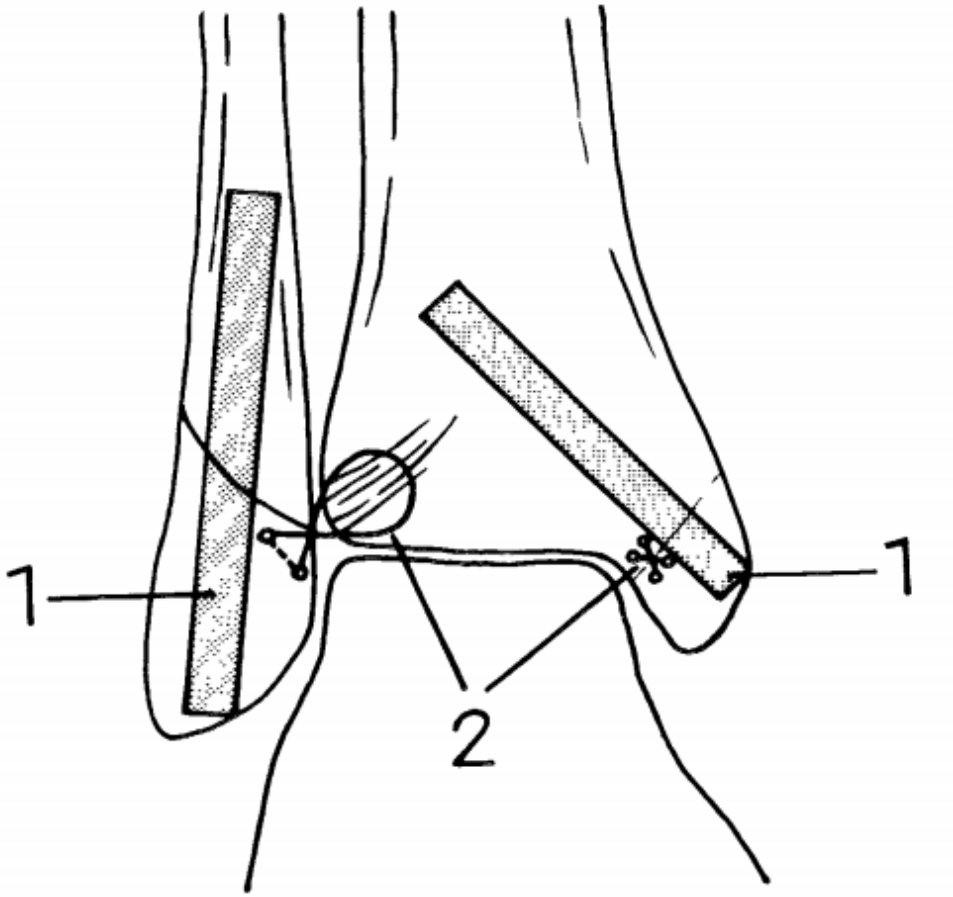

Figure (8): The biodegradable rods (1) are placed within the cancellous bone in drill channels across the fracture surfaces. The fixation is reinforced by eight polylactide-glycolide sutures (2) [(62)]

G) An **implant for scaphoid nonunions** made of poly-L-lactic acid showed very good results, with the average time of bone union being 4.5 months (range of 3.5 to 7 months) without adverse reactions at the site of implantation.[63]

F) Amorphous semicrystalline poly-D, L-lactic acid (PDLLA) has been used to develop arterial remodeling technologies including bioresorbable scaffolds (ART-BRSs) for drug eluting stents. According to the mechanisms of degradation, the terms bioabsorbable and bioresorbable were also used as drug-eluting stents (DESs). These DESs may be divided into two types: completely absorbable (biodegradable) and permanent (non-biodegradable), the latter of which contains a scaffold coated with a biodegradable polymer called a biodegradable system.[64-73] A completely biodegradable

stent has many advantages over non-biodegradable DESs. A drug-eluting bioresorbable vascular scaffold (DEBVS) functions as a scaffold, and is then reabsorbed naturally and metabolized by the body when no longer needed.

The advantages to DEBVS therapy have been discussed in more recent literature.[66,68,74,75] ABSORB was a single-arm, prospective, open-label, clinical study in humans following safety and imaging end points for a bioresorbable implanted drug delivery system. After two years of follow-up, a fully bio-resorbed is recorded, lumen enlargement (which is associated with minimized plaque burden) was noted, and vasomotion was recuperated to the coronary artery native state. DESs caused a revolution in the treatment of coronary artery disease, with only very minor, late adverse effects reported in patients.

The recuperation of vasomotion and the obscurity of the foreign body reaction are evidence of a healthy vessel and indicate that the risk of stent thrombosis in the late stage has been reduced. More studies are need to confirm the last findings,[76,77] to choose the material and to design the biodegradable scaffold. Using amorphous semicrystalline PDLLA polymers to design bioresorbable scaffolds, positive remodeling (vessel enlargement) has been demonstrated between 3 and 6 months. No anti-proliferative drug has occurred.[78,79]

2- Neutralized glass ceramic (GB9N), porous alpha-tricalcium phosphate (α-TCP) ceramics, (polylacid/gycolid/GB9N) composition and solvent-dehydrated human bone

An *in vitro* study was performed to illustrate the release and adsorption behavior of a number of growth factors dispersed in different biodegradable implant formulations. The biodegradable formulations included neutralized glass ceramic (GB9N), porous alpha-tricalcium phosphate (α-TCP) ceramics, (polylacid/gycolid/GB9N) composition, and solvent-dehydrated human bone (SDB). The growth factors investigated were recombinant human basic fibroblast growth factor (rhbFGF), bone morphogenetic protein-4 (rxBMP-4), and recombinant human vascular endothelial growth factor (rhVEGF).

Scaffolds had the dimensions of 7 x 7 x 10mm, in which 5μg of growth factors were dispersed in 150mL of phosphate-buffered saline (PBS). Iodine was used to label the growth factor to analyze the amount released and adsorbed. The adsorption behavior and the maximum amount of growth factors that could be adsorbed (**Figure 9**) depended on the nature of the tested materials and the growth factor itself.[80] The lower limit of the solvent dehydrated bone (SDB) adsorption may have been so due to the higher porosity and minor overall surface compared with the other formulations. In contrast, the main reasons for the lower adsorption of rhbFGF on α-TCP and GB9N were due to the physical and chemical properties.[80]

The release behavior of growth factors from the implants **(Figure 10)** was very rapid during the first hour due to elution of the non-adsorbed protein, followed by a long-lasting release. The physical and chemical interaction of the matrix and growth factors affected the controlled release stage.[80] The polymers broke down slowly after implantation into living tissue or came into contact with water by hydrolytic reactions.[80] Reabsorption of degradation products by the body occurs.[81] The *in vitro* study illustrates the importance of using these biodegradable implants as carriers for estrogenic growth factors.

3- Hyaluronic acid-tyramine conjugates:

A formula was created to design a biocompatible and biodegradable injectable hydrogel delivery system. The backbone of that hydrogel was hyaluronic acid, which is a glycosaminoglycan made of repeated units of disaccharides (b-1,4-D-glucuronic acid and b-1,3-N-acetyl-D-glucosamine).[82] Hyaluronic acid-tyramine (HA-Tyr) conjugates are synthesized using peroxidase-catalyzed oxidation reactions (**Figure 11)** and are used to develop biocompatible and very simple *in situ* gel-forming systems.[83]

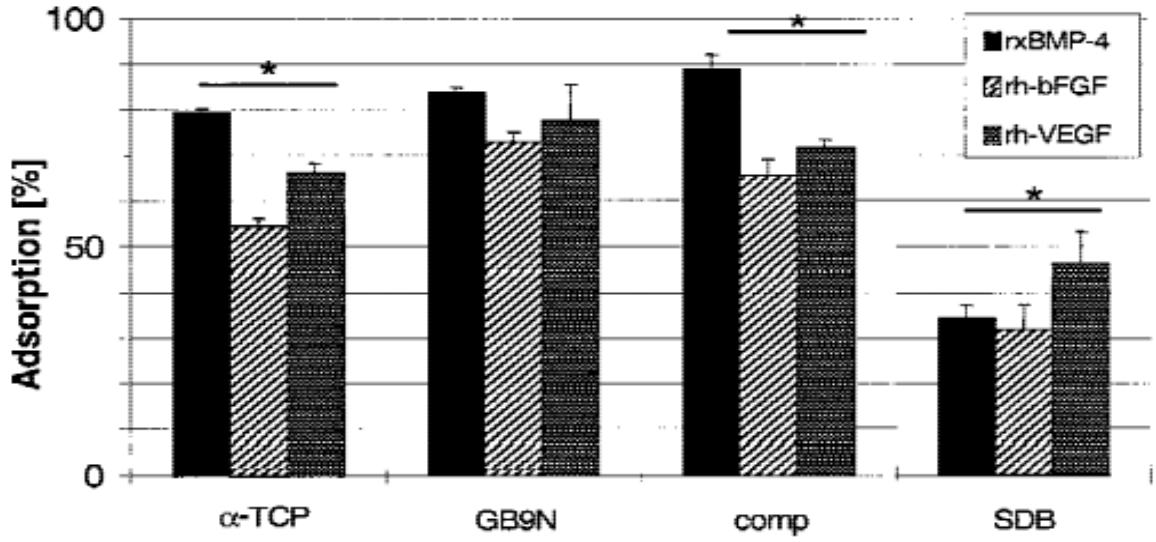

Figure (9): The growth factors adsorption to alpha-tricalcium phosphate (α-TCP), glass ceramic (GB9N), composite (comp) and solvent dehydrated bone (SDB) [79]

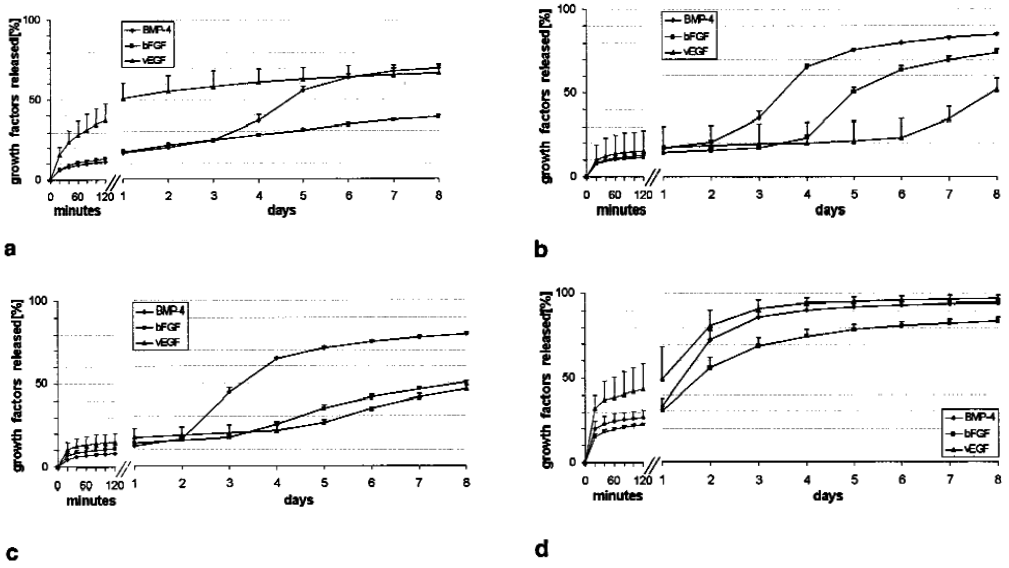

Figure (10): The cumulative release of rxBMP-4, rh-bFGF, and rh-VEGF from alpha tricalcium phosphate (a), GB9N (b), composite (c), and solvent-dehydrated human bone (d) versus time [79]

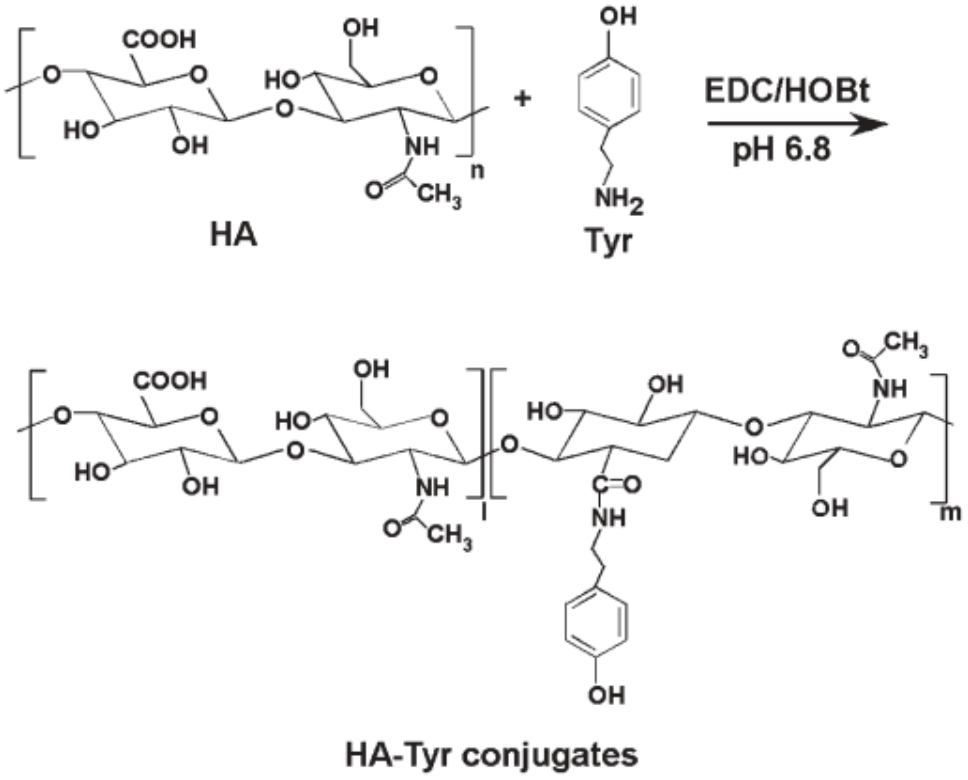

Figure (11): HA-Tyr conjugates Synthesis [82]

In vivo, a hydrogel was formed by injecting two solutions of HA-Tyr via syringes, the first solution consisting of H_2O_2 as an oxidant of horseradish peroxide (HRP), and the second solution consisting of HRP as a model catalyst used to stimulate the oxidative coupling of the phenol moiety in the body (**Figure 12**). This yielded a hydrogel compatible with the bioactive agent without causing any inflammation or any excess reactions[83]. The gel strength and gelation time were modulated by changing the concentrations of H_2O_2 and HRP. With 1.25 unit/mL of HRP and 2.4 mmol/L of H_2O_2, the hydrogels were formed within 20 seconds (**Figure 13)**.[82]

The biodegradation of hydrogels with a size of 20 x 20 x 1.2mm was studied *in vitro* at different concentrations of hyaluronidase by recording the weight loss of the implant. All the hydrogels degraded completely in the presence of hyaluronidase, and no considerable change in the weight in the absence of hyaluronidase was observed (**Figure 14**). This linear relationship between time and biodegradation may be explained by the degradation (surface erosion only), it is expected that this degradation behavior of hydrogels may lead to sustained release of bioactive agents resembling proteins that would be released only according to the degradation of surface.[83]

4-Poly(ethylene oxide) and poly(L-lactic acid) copolymer

Poly (ethylene oxide) (PEO) and poly (L-lactic acid) (PLLA) blocks are used to design a thermosensitive, solvent-free (no organic solvent) and injectable biodegradable implant. The temperature-dependent, reversible sol-gel transition is obtained when forming an aqueous solution of these copolymers. The bioactive agent may be dispersed in the aqueous phase of the hydrogel. The aqueous phase is heated to an elevated temperature (around 45 °C), and is then injected subcutaneously.

Because body temperature is less than the temperature of the aqueous phase by about 8 °C, rapid cooling occurs, and the aqueous solution phase transforms into a gel, providing a sustained-release matrix for bioactive agents.[84] However, the high injection temperature (45 °C) may limit the usage of this system, particularly for thermolabile biological agents and proteins.

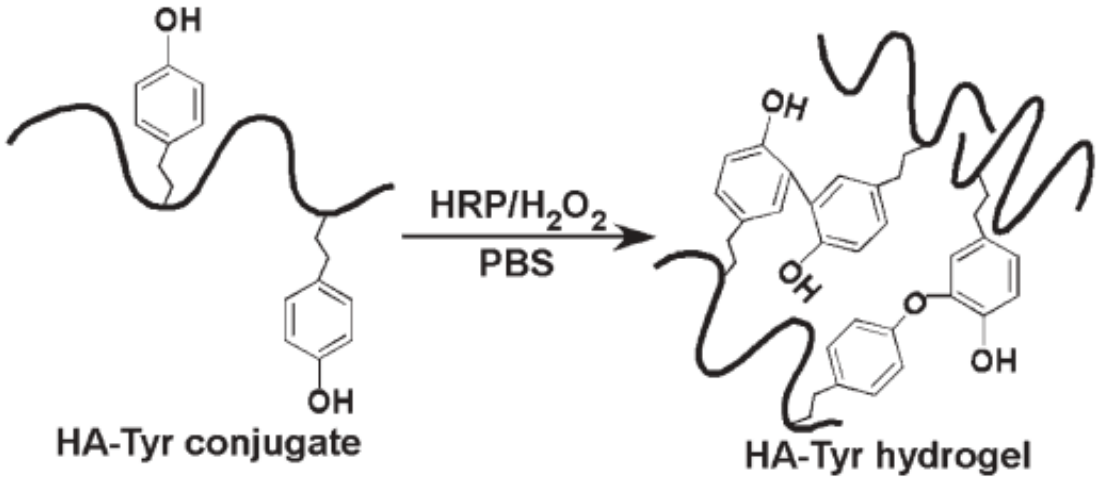

Figure (12): The in situ gel forming via HA-Tyr conjugates oxidation by enzyme- catalyzed oxidation reaction [82]

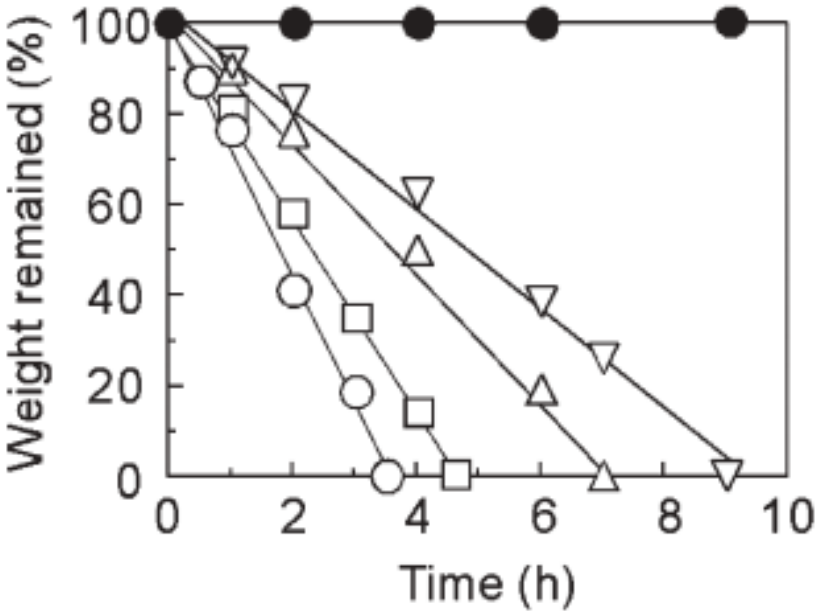

Figure (14): *In-Vitro* enzymatic degradation of HA-Tyr hydrogels in PBS at 37 Co. Hyaluronidase concentration: O, 100 unit ml-1 ;□, 50 unit ml-1; ∆, 25 unit ml-1; ▼, 10 unit m-1 ; ●, 0 unit ml-1 [82]

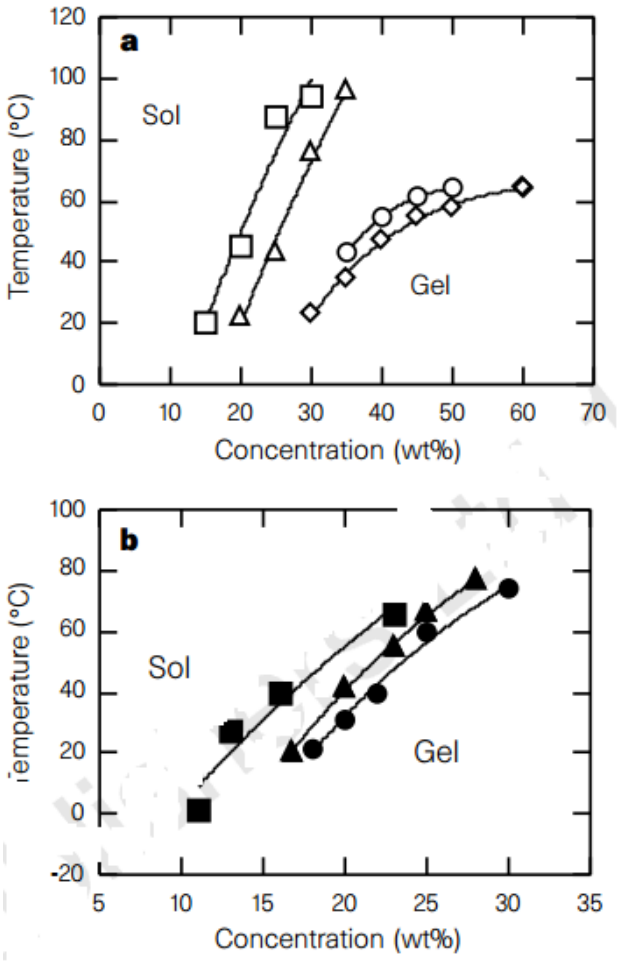

Figure (15): Gel–sol transition curves. a, PEO–PLLA diblock copolymers with Mr values as follows: diamonds, 5,000–720; circles, 5,000–1,000; triangles, 5,000– 1,730; squares, 5,000–1,960. b, PEO–PLLA–PEO triblock copolymers with *Mr* values as follows: filled circles, 5,000 2,040–5,000; filled triangles, 5,000–3,000– 5,000; filled squares, 5,000–5,000–5,000 (84)

The sol-gel process is a technique used to prepare transparent oxide glasses by hydrolysis and polycondensation of alkoxide. Little to no heating is required and, consequently, the gel may be doped with molecules whose poor thermal stability precludes their incorporation in traditional inorganic hosts. Such molecules become entrapped in the growing covalent gel network rather than being chemically bound to the inorganic matrix. The process may be divided into the following steps: forming a solution, gelation, aging and drying,

The temperature of the sol-gel transition can be modulated by changing the concentration and composition of the copolymer blocks. Increasing the concentration and/or length of block composition may increase aggregation tendency in water. Hence, the onset of gel formation and the incline of the gel-sol transition curve begin at a lower concentration as shown in **Figure 15**.[84]

This system may be used to deliver biological agents with high molecular weights (MWs), such as proteins with

a limited diffusion coefficient. It may also be used for hydrophobic drugs of low molecular weight. The release of dextran (MW: 20,000) as a model drug labeled with fluorescein isothiocyanate (FITC) was studied *in vitro*. The presence of drug affected the temperature at which gel-sol transition occurred. The bioactive drug was dispersed in the polymer at 45 °C, resulting in a solution phase that was then cooled to 37 °C and administered by subcutaneous injection. The solutes released from the gel form were detected by fluorescence spectroscopy and plotted as a function of time (**Figure 16**).

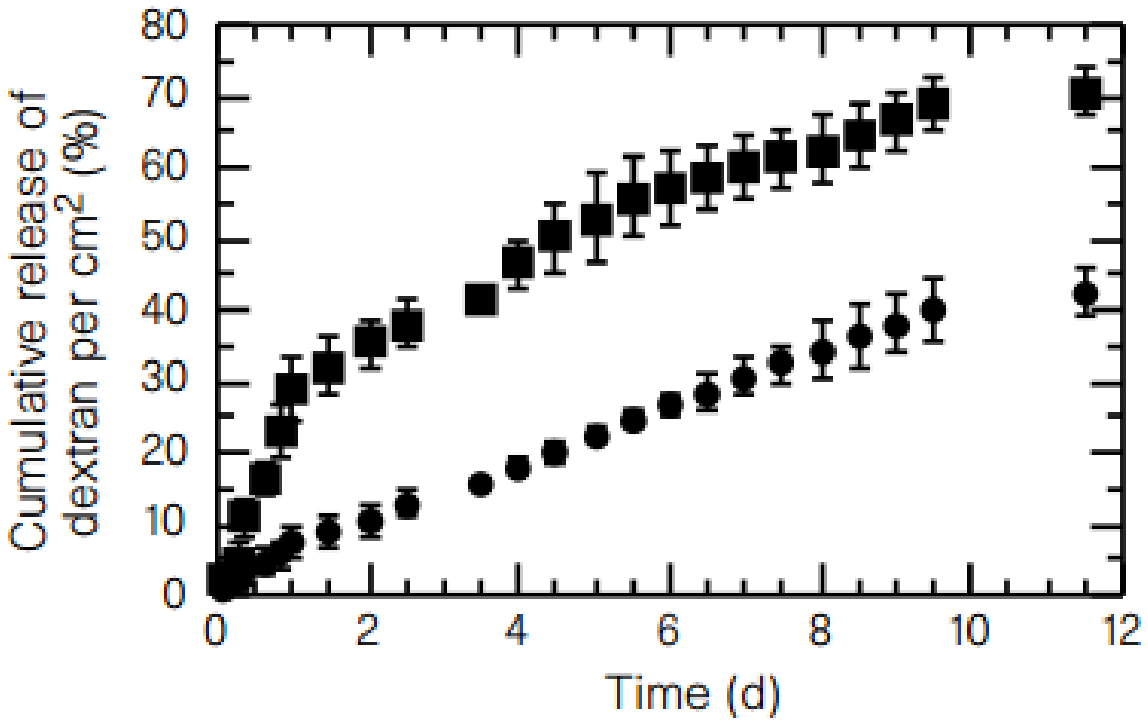

Figure (16): In-*Vitro* release profile of FITC-labelled dextran (Mr 20,000) from PEO– PLLA–PEO (Mw 5,000–2,040–5,000) triblock copolymer. FITC-labelled dextran (5.4mg) was mixed with 0.5ml of aqueous polymer solution (filled squares, 23wt%; filled circles, 35wt%). The mixture was injected into a 3.0-ml cuvette which was incubated in a 37Co water bath and 2.5ml of distilled water was added. The area of the gel exposed to the water was 0.4cm2. With stirring, 1.0ml of sample was taken at designated times and the same amount of distilled water was added. The amount of FITC-dextran released was calculated measurements of fluorescence intensity (excitation wavelength, 495nm; emission wavelength, 515nm) after dilution [(84)]

Initial loading, molecular weight, concentration of the polymer, and the degree of hydrophobicity of the drug are all factors that control the release rate of drug from this system. Dextran is highly water-soluble. As shown in **Figure 16**, there is an inverse relationship between polymer concentration and drug release rate. Over the course of 12 days, whereas more than 70% of dextran was released from the 23% (wt/wt) gel, only 40% of dextran was released from the 35% (wt/wt) gel. It was deduced that the protein or hydrophobic drug required one month to be completely released.

At the beginning, the drug is released due to diffusion, then diffusion and degradation mechanisms are involved in the drug release. PEO, PLLA and their degradation products are biocompatible and biologically and pharmacologically inactive.[85,86]

This system of PEO and PLLA blocks has many advantages, including a simple formula, ability to store the matrix in solid or dry form at less than room temperature prior to administration, avoidance of organic or toxic solvents, and avoidance of surgical procedures to insert the implant.[84] In addition, the material is quenched to body temperature within a few seconds, so no inflammation, pain or tissue damage is observed after subcutaneous administration.[84]

5-Chitosan-polyol salt combination

This system provides a biocompatible and biodegradable implant solution of gels *in situ* with a change in medium temperature. Chitosan-polyol salt combinations are used to form temperature-sensitive, neutral solutions that exhibit the liquid phase below room temperature, and in which living cells and therapeutic proteins may also be encapsulated. Then, upon subcutaneous injection into the target tissue, a monolithic gel implant forms *in situ* at body temperature.

Chitosan is a pH-dependent cationic polymer, which means that it remains a solution at pH values below 6.2, but transforms to a hydrated gel-like precipitate at higher pH values.[87] The addition of polyol salt (glycerol phosphate disodium salt) changes chitosan from a pH-dependent solution into a temperature-controlled, pH-dependent solution (**Figure 17**). Therefore, when it is below room temperature, the matrix of the implant remains in the solution phase even at a physiological pH, but is transformed into a gel if injected to the temperature of the body.[87]

This system has been used to encapsulate biologically active growth factors and living chondrocytes for tissue engineering. In addition to subcutaneous injection, it may be administrated intramuscularly, intra-articularly, in the cul-de-sac of the eye, and in bone and cartilage defects.[87]

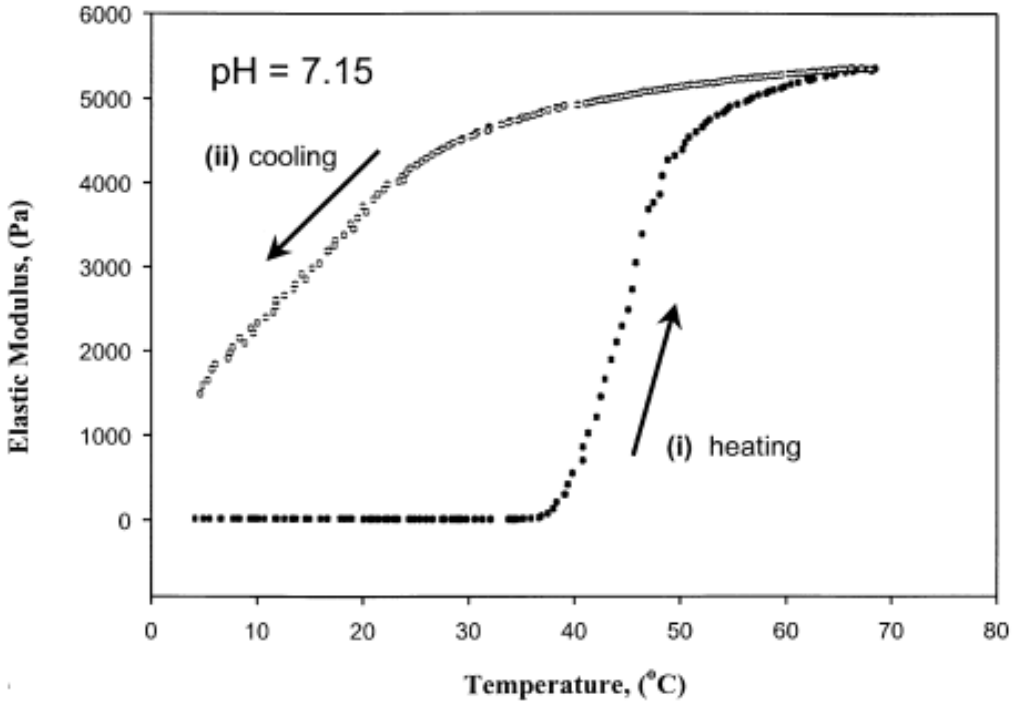

Figure (17): Sol/gel transition of typical C/GP solutions at the physiological pH [87]

6- Poly (methylidene malonate) (PMM2.1.2)

This synthetic polymer was used to develop a biodegradable implant as a scleral disc to release triamcinolone acetonide (TA). High molecular weight PMM2.1.2 (100,000 to 150,000 Da) associated with ethoxylated derivatives of stearic acid (Simulsol®) or oligomers of methylidene malonate (as plasticizer) showed good mechanical properties for implantation *in vivo*. After insertion, the implant showed good biocompatibility and did not cause any abnormal inflammation. Release studies of *TA* showed that the implant maintained the drug concentration through the effective level in the vitreous and sclera throughout five weeks[92].

7- PEG-oligoglycolyl-acrylates and eosin dye

A photopolymerizable, biodegradable hydrogel was fabricated as a tissue contact material and controlled-release carrier. This formula consists of a macromer with at least two free radical-polymerizable regions (PEG-oligoglycolyl-acrylates) and a photosensitive initiator (eosin dye). Visible light or ultraviolet light is used as a light source. After the injection of the formula, the light source is directed to the mixture of macromer and photoinitiator. This exposure leads to rapid cross-linking and network formation. This network is useful for entrapping hydrophilic drugs and enzymes to deliver them in a controlled-release manner.[93] The polymerization is affected by the light source; polymerization takes less time and the physical properties of the polymer is improved when using argon laser as a light source.[94]

There are many advantages of using this technique, including a rapid polymerization rate at physiological temperatures, and ability to form the exact shape needed since the initial material is liquid solution and moldable putties.[95] These advantages encourage the use of this system for tissue engineering,[96] orthopedic application,[97] cell transplantation[98] and local drug delivery.[99]

8- Alginate

Alginate is a natural polymer. Upon contact with divalent cations (e.g., calcium ions), it transforms *in situ* from a liquid phase to a gel phase. A fluid suspension is fabricated to consist of thermally sensitive Ca^{+2} loaded vesicles and sodium alginate. Upon subcutaneous administration, it is transformed to a gel due to the effect of body temperature (37 °C). The slow seeping of calcium from liposomes and the large amount of drug release leads to a short half-life, which is considered a disadvantage of this system.[100]

For ocular administration, alginate has been used to create an eye gel implant. Ca^{+2} ions are naturally available in the eye fluid at enough concentration (0.008%, w/v) to induce gelation of an alginate-pilocarpine solution, providing sustained release of pilocarpine.[101] The Ca^{+2}-alginate system is limited due to its potential immunogenicity and the longer amount of time needed for degradation *in vivo*.[102,103]

9-Polyanhydride (Polifeprosan 20®) copolymer

Polifeprosan 20® is the trade name of a biodegradable polyanhydride copolymer. The chemical structure (**Figure 18**) consists of poly[bis(p-carboxyphenoxy)propane] and sebacic acid in a 20:80 molar ratio. Gliadel® wafers are an example of a biodegradable implanted drug delivery system of carmustine used for the treatment of brain cancer.[104] In each Gliadel® wafer, the drug (carmustine 7.7mg) is distributed uniformly in the matrix of the copolymer (Polifeprosan 20® 192.3 mg). The biodegradable polyanhydride disks are dime-sized, 1-mm thick and 1.45 cm in diameter.

The implant delivers carmustine directly into the surgical cavity generated after the removal of a tumor. Up to 8 wafers are inserted along the floor and wall of the cavity. Carmustine, carboxyphenoxypropane, and sebacic acid are released from the implant. When carmustine is released from each wafer, it diffuses to the surrounding brain tissue for an exact therapeutic dose.[105] Because of the compatibility of implants with the aqueous environment of the surgical cavity, hydrolysis of anhydride bonds occurs. Within three weeks, 70% of the copolymer breaks down to its monomers.[7]

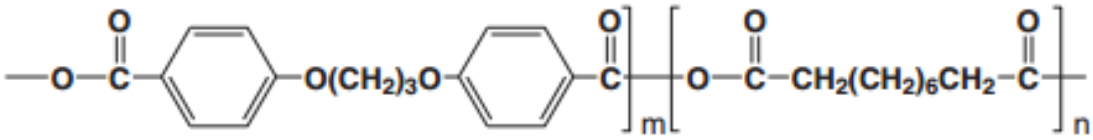

Figure (18): Chemical structure of Polifeprosan 20 copolymer (ratio n:m 20:80) [7]

10- Magnesium-based metallic bioresorbable scaffolds

The angiographic results instantly obtained were similar to those of metallic stents. After implantation, a few weeks were needed to lose the radial support. It needs a high rate of recoil and constrictive remodeling to be done. Although the device has certain mechanical insufficiencies and does not elute any anti-proliferative drug, there were no deaths, myocardial infarctions, or stent thromboses observed. This study suggests that the magnesium scaffold was safe, but due to the loss of mechanical support and uncontrolled neointima proliferation, it lacks efficacy.[106]

11- Desaminotyrosine polycarbonate

Desaminotyrosine polycarbone is a bioresorbable and radiopaque polymer used to design bioresorbable scaffolds (e.g., the ReZolve devices). The study showed no vessel recoil. However, there was a high rate of in-stent late lumen loss.[107]

12- Polydioxanone (PDS) polymer

This biodegradable polymer has been studied *in vivo*, illustrating its use in internal orbital wall reconstruction. Studies have shown no muscle entrapment within the fracture line, and the orbital volume was not reduced. However, in some cases, thick scar formation was reported. It was shown that this system is not suitable to treat internal orbital wall reconstruction.[108]

13- Trimethylene carbonate (TMC) polymer

The degradation and tissue response of trimethylene carbonate (TMC) after subcutaneous implantation of TMC films in rats were investigated. The TMC films showed extensive degradation after 3 weeks of implantation, and less than one year was required to obtain complete resorption. The *in vivo* study showed that the degradation process occurred due to surface erosion, and that this polymer is biocompatible. Mixing this polymer with 52% (mole/mole) D,L-lactide (DLLA) or 89% (mole/mole) Ɛ-caprolactone (CL) made the polymer suitable for fabrication of short and long biodegradable devices for soft tissue engineering.[109]

14- Poly (ortho ester) (POE) polymer

Bioabsorbable POEs, based on two diols (trans-cyclohexane-dimethanol and 1,6-hexanediol) and a diketene acetal, 3,9-bis(ethylidene-2,4,8,10-tetraoxaspiro[5,5]undecane), may be fabricated easily by both hot compression molding and solvent casting. (**Figure 19**) illustrates the steps for POE synthesis.

The POE polymer is hydrophobic. After exposure, it maintains its properties longer than the polyester polymers. Surface hydrolysis is the main mechanism of its degradation. The degradation process leads to non-acidic degradation products, and eventually to alcoholic and acidic products (**Figure 20**). Over the course of 31 days, a reduction in weight was observed without any change in water absorption or molecular weight.[110]

15- Cholesterol and lecithin (C:L)

The use of cholesterol and lecithin (C:L) to fabricate biodegradable implants may be used to deliver veterinary vaccines. For example, they have been used to deliver recombinant antigen *Dichelobacter Nodosus* pili and adjuvant Quil A to sheep. Implants with dimensions of 5.5mm x 1.8mm were inserted subcutaneously and compared with a conventional vaccination regimen of two injections four weeks apart.

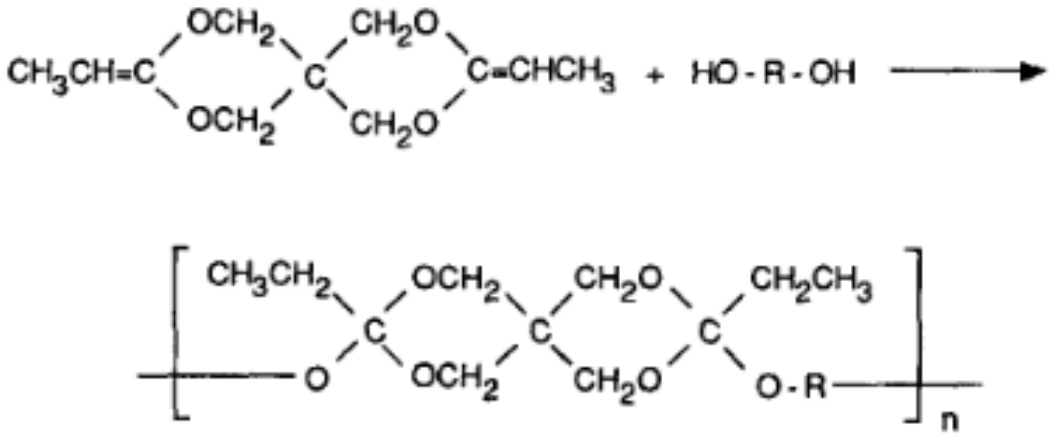

Figure (19): Synthesis of polyorthoester polymers [110]

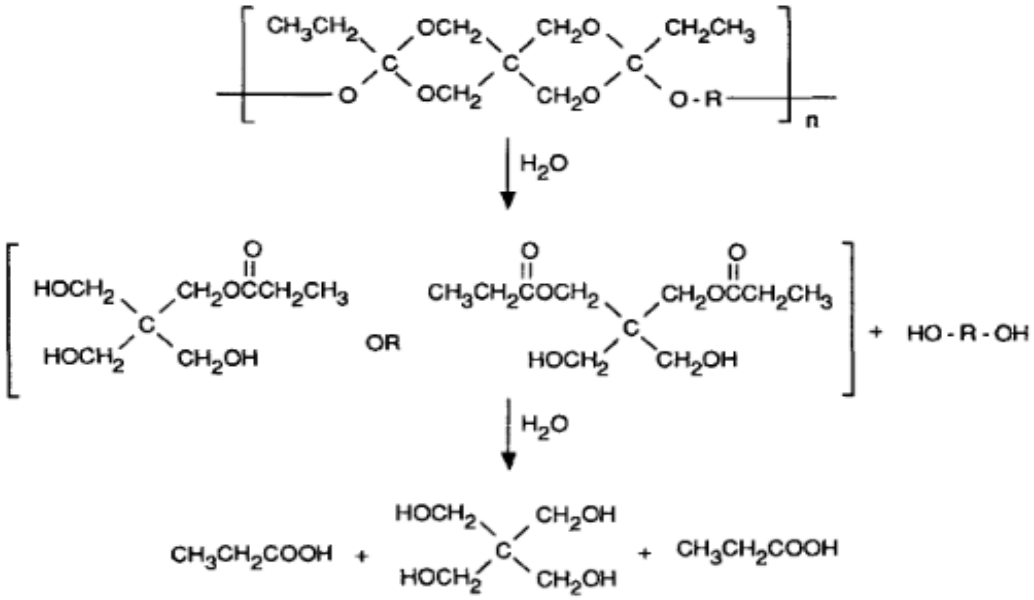

Figure (20): Hydrolytic degradation of poly(orth ester) [110]

To deliver a priming dose and a boosting dose of antigen, two implanted systems were used at the same time: a simple implant and an implant coated with C:L. The double implant caused stimulation of antibody equivalent to the stimulation obtained by the conventional vaccination regimen after six weeks. Then, the antibody level dropped significantly. The implants showed evidence of degradation over the experimental period. The reactions at the site of implantation were less severe and resolved faster with the implants compared to the injected vaccines.[111] In addition, it was found that the presence of Quil A increased the amount of antigen released after 24hr from 29% to 44%.

Table 2. Ophthalmic preparations, brand names, used material, active agents, duration of drug release, characteristics, and eye diseases (51)-(61)

Brand name	Materials	Active agent	Duration of drug release	Characteristic	Eye diseases
Surodex™ [50]–[56]	PLGA,HPMC	Dexamethasone (60Mg)	7-10 days	Biodegradable pellet	Post operative inflammation following cataract surgery (phase 3)
Ozurdex® [57], [58]	PLGA	Dexamethasone (0.7mg)	6 months	Biodegradable rod-shape intravitreal implant	Macular edema following branch RVO or central RVO[a]
Lacrisert® [59]	HPC	HPC (mg)	1 day	Biodegradable translucent, rod-shaped, water soluble insert	Moderate to severe dry eye syndrome including keratitis sicca
IBI 20089 verisome™ [60], [61]	Proprietary	Triamcinolone acetate (6.9-13.8 mg)	Up to one year	Biodegradable	CME associated with retinal vain occlusion and post operative cataract surgery

16- Non-polymeric technology

Verisome™ drug delivery technology is a versatile system for controlled, extended-release of therapeutic agents, such as small molecules, peptides, proteins and monoclonal antibodies for ocular administration. Studies on rabbits using a single intravitreal injection of IBI-20089 (a triamcinolone controlled-release formulation by Icon Bioscience), formulated with the Verisome™ technology delivered triamcinolone acetonide (TA) at a mean daily dose of 1.1µg/mL for up to one year.[112] IBI-20089 was studied to evaluate its safety and efficacy in a phase 1 trial in 10 patients with cystoid macular edema associated with retinal vein occlusion, and the system was well-tolerated by the rabbit eye.[60,113]

CONCLUSION

The biodegradable implant drug delivery system (BIDDS) has many advantages over conventional drug delivery systems, such as non-biodegradable implants and parenteral dosage forms. Various biological agents and proteins that are challenging to fabricate using conventional dosage forms have been successfully incorporated in BIDDS. BIDDS provides controlled release of drugs over the period of treatment. Patient adherence may be improved due to decreased dosing frequency and avoidance of a second surgery for implant removal at the end of therapy. The complexity and high cost-to-benefit ratio are the main challenges that limit the use of BIDDS. New, synthetic degradable polymers with lower cost and better safety profiles are promising for current and future clinical applications.

REFERENCES

(1) J. Heller, "Controlled release of biologically active compounds from bioerodible polymers," *Biomaterials*, vol. 1, no. 1, pp. 51-57, Jan. 1980.

(2) R.S. Langer and N. A. Peppas, "Present and future applications of biomaterials in controlled drug delivery systems," *Biomaterials*, vol. 2, no. 4, pp. 201–214, Oct. 1981.

(3) D.A. Wood, "Biodegradable drug delivery systems," *International Journal of Pharmaceutics*, vol. 7, no. 1, pp. 1–18, 1980.

(4) JudyH Senior, "Rationale for Sustained-Release Injectable Products," in *Sustained-Release Injectable Products*, 0 vols., CRC Press, 2000, pp. 1–11.

(5) Y. Shi and L. C. Li, "Current advances in sustained-release systems for parenteral drug delivery," *Expert Opin Drug Deliv*, vol. 2, no. 6, pp. 1039–1058, Nov. 2005.

(6) S. S. Iyer, W. H. Barr, and H. T. Karnes, "Profiling in vitro drug release from subcutaneous implants: a review of current status and potential implications on drug product development," *Biopharm Drug Dispos*, vol. 27, no. 4, pp. 157–170, May 2006.

(7) L. W. Kleiner, J. C. Wright, and Y. Wang, "Evolution of implantable and insertable drug delivery systems," *J Control Release*, vol. 181, pp. 1–10, May 2014.

(8) B. D. Ratner, "Reducing capsular thickness and enhancing angiogenesis around implant drug release systems," *Journal of Controlled Release*, vol. 78, no. 1–3, pp. 211–218, Jan. 2002.

(9) J. E. Sanders, S. D. Bale, and T. Neumann, "Tissue response to microfibers of different polymers: Polyester, polyethylene, polylactic acid, and polyurethane," *J. Biomed. Mater. Res.*, vol. 62, no. 2, pp. 222–227, Nov. 2002.

(10) J. Folkman and D. M. Long, "The use of silicone rubber as a carrier for prolonged drug therapy," *Journal of Surgical Research*, vol. 4, no. 3, pp. 139–142, Mar. 1964.

(11) K. Heilmann, *Therapeutic systems*. Georg Thieme, 1978.

(12) A. J. Domb, M. Maniar, and A. S. T. Haffer, "Biodegradable polymer blends for drug delivery," US5919835 A, 06-Jul-1999.

(13) R. A. Jain, "The manufacturing techniques of various drug loaded biodegradable poly(lactide-co-glycolide) (PLGA) devices," *Biomaterials*, vol. 21, no. 23, pp. 2475-2490, Dec. 2000.

(14) J.C. Middleton and A.J. Tipton, "Synthetic biodegradable polymers as orthopedic devices," *Biomaterials*, vol. 21, no. 23, pp. 2335–2346, Dec. 2000.

(15) Maarten van der Zee, "Chapter 1: Biodegradability of Polymers Mechanisms and Evaluation Methods | IHS Engineering360," 2000. [Online]. Available: http://www.globalspec.com/reference/49117/203279/chapter-1-biodegradability-of-polymers-mechanisms-and-evaluation-methods. [Accessed: 22-Oct-2015].

(16) D. Shuwisitkul, "Biodegradable implants with different drug release profiles : Bioabbaubare Implantate mit verschiedenen Arzneistoff-Freisetzungsprofilen." Berlin: Freie Universität Berlin Universitätsbibliothek, 2011.

(17) anon, "Cyanamid research develops world's first synthetic absorbable suture.," 1970.

(18) D.H. Lewis, "Controlled release of bioactive agents from lactide/glycolide polymers," *Drugs and the pharmaceutical sciences*, vol. 45, pp. 1–41, 1990.

(19) O. Pillai and R. Panchagnula, "Polymers in drug delivery," *Current Opinion in Chemical Biology*, vol. 5, no. 4, pp. 447–451, Aug. 2001.

(20) K. Y. Lee and S. H. Yuk, "Polymeric protein delivery systems," *Progress in Polymer Science*, vol. 32, no. 7, pp. 669–697, Jul. 2007.

(21) L.S. Liu, S.-Q. Liu, S. Y. Ng, M. Froix, T. Ohno, and J. Heller, "Controlled release of interleukin-2 for tumour immunotherapy using alginate/chitosan porous microspheres," *Journal of Controlled Release*, vol. 43, no. 1, pp. 65–74, Jan. 1997.

(22) H. Ringsdorf, "Structure and properties of pharmacologically active polymers," *J. polym. sci., C Polym. symp.*, vol. 51, no. 1, pp. 135–153, Jan. 1975.

(23) C. Mungiu, D. Gogălniceanu, M. Leibovici, and I. Negulescu, "On the medical use of cyanoacrylic esters: Toxicity of pure n-butyl-α-cyanoacrylate," *J. polym. sci., C Polym. symp.*, vol. 66, no. 1, pp. 189–193, Jan. 1979.

(24) J. T. Santini, M. J. Cima, and R. Langer, "A controlled-release microchip," *Nature*, vol. 397, no. 6717, pp. 335–338, Jan. 1999.

(25) P. Gardner, "Microfabricated nanochannel implantable drug delivery devices: trends, limitations and possibilities," *Expert Opinion on Drug Delivery*, vol. 3, no. 4, pp. 479–487, Jul. 2006.

(26) E. E. Nuxoll and R. A. Siegel, "BioMEMS devices for drug delivery," *IEEE Engineering in Medicine and Biology Magazine*, vol. 28, no. 1, pp. 31–39, Jan. 2009.

(27) T. Higuchi, "Mechanism of sustained-action medication. Theoretical analysis of rate of release of solid drugs dispersed in solid matrices," *J. Pharm. Sci.*, vol. 52, no. 12, pp. 1145–1149, Dec. 1963.

(28) D. R. Paul and S. K. McSpadden, "Diffusional release of a solute from a polymer matrix," *Journal of Membrane Science*, vol. 1, pp. 33–48, 1976.

(29) C.-C. Chu, "Biodegradable polymers: an overview," *Encyclopedia of biomaterials and biomedical engineering. New York: Informa Healthcare USA, Inc*, pp. 195–206, 2008.

(30) B. R. Conway, "Recent patents on ocular drug delivery systems," *Recent patents on drug delivery & formulation*, vol. 2, no. 1, pp. 1–8, 2008.

(31) A. Kumari, S.K. Yadav, and S.C. Yadav, "Biodegradable polymeric nanoparticles based drug delivery systems," *Colloids and Surfaces B: Biointerfaces*, vol. 75, no. 1, pp. 1–18, 2010.

(32) *Encyclopedia of Biomaterials and Biomedical Engineering, 4 Volume Set, Second Edition*, 2 edition. CRC Press, 2008.

(33) Lee, P. Hughes, A. D. Ross, and M. R. Robinson, "Biodegradable Implants for Sustained Drug Release in the Eye," *Pharm Res*, vol. 27, no. 10, pp. 2043–2053, Jun. 2010.

(34) null Shive and null Anderson, "Biodegradation and biocompatibility of PLA and PLGA microspheres," *Adv. Drug Deliv. Rev.*, vol. 28, no. 1, pp. 5–24, Oct. 1997.

(35) R. Gaudana, J. Jwala, S. H. Boddu, and A. K. Mitra, "Recent perspectives in ocular drug delivery," *Pharmaceutical research*, vol. 26, no. 5, pp. 1197–1216, 2009.

(36) V. R. Kearns and R. L. Williams, "Drug delivery systems for the eye," *Expert review of medical devices*, vol. 6, no. 3, pp. 277–290, 2009.

(37) T. Yasukawa, Y. Ogura, H. Kimura, E. Sakurai, and Y. Tabata, "Drug delivery from ocular implants," 2006.

(38) N. H. Shah *et al.*, "A biodegradable injectable implant for delivering micro and macromolecules using poly (lactic-co-glycolic) acid (PLGA) copolymers," *Journal of Controlled Release*, vol. 27, no. 2, pp. 139–147, Nov. 1993.

(39) "Zoladex - zoladex3_6.pdf." .

(40) "Zoladex - zoladex10_8.pdf." .

(41) K. Bhise, V. Kotwal, M. Saifee, and N. Inamdar, "Biodegradable polymers: Which, when and why?," *Indian Journal of Pharmaceutical Sciences*, vol. 69, no. 5, p. 616, 2007.

(42) R.D. Jager, L. P. Aiello, S. C. Patel, and E.T. Cunningham, "Risks of intravitreous injection: a comprehensive review," *Retina (Philadelphia, Pa.)*, vol. 24, no. 5, pp. 676–698, Oct. 2004.

(43) F.R. Stefanini, J.F. Arevalo, and M. Maia, "Bevacizumab for the management of diabetic macular edema," *World J Diabetes*, vol. 4, no. 2, pp. 19–26, Apr. 2013.

(44) G. G. Giordano, P. Chevez-Barrios, M. F. Refojo, and C. A. Garcia, "Biodegradation and tissue reaction to intravitreous biodegradable poly (D, L-lactic-co-glycolic) acid microspheres," *Current eye research*, vol. 14, no. 9, pp. 761-768, 1995.

(45) T. Moritera *et al.*, "Biodegradable microspheres containing adriamycin in the treatment of proliferative vitreoretinopathy," *Investigative Ophthalmology and Visual Science*, vol. 33, pp. 3125–3125, 1992.

(46) T. Moritera, Y. Ogura, Y. Honda, R. Wada, S. H. Hyon, and Y. Ikada, "Microspheres of biodegradable polymers as a drug-delivery system in the vitreous," *Invest Ophthalmol Vis Sci*, vol. 32, no. 6, pp. 1785–90, 1991.

(47) By, "Allergan Announces FDA Approves Revised Indication for OZURDEX® (dexamethasone intravitreal implant) 0.7 mg for the Treatment of Diabetic Macular Edema," *MarketWatch*. [Online]. Available: http://www.marketwatch.com/story/allergan-announces-fda-approves-revised-indication-for-ozurdex-

dexamethasone-intravitreal-implant-07-mg-for-the-treatment-of-diabetic-macular-edema-2014-09-29. [Accessed: 23-Oct-2015].

(48) N. Kunou *et al.*, "Long-term sustained release of ganciclovir from biodegradable scleral implant for the treatment of cytomegalovirus retinitis," *J Control Release*, vol. 68, no. 2, pp. 263–271, Aug. 2000.

(49) S. Eperon, L. Bossy-Nobs, I. K. Petropoulos, R. Gurny, and Y. Guex-Crosier, "A biodegradable drug delivery system for the treatment of postoperative inflammation," *Int J Pharm*, vol. 352, no. 1–2, pp. 240–247, Mar. 2008.

(50) D. F. Chang, I. H. Garcia, J. D. Hunkeler, and T. Minas, "Phase II results of an intraocular steroid delivery system for cataract surgery," *Ophthalmology*, vol. 106, no. 6, pp. 1172-1177, 1999.

(51) S.S. Lee, P. Yuan, and M. R. Robinson, "Ocular implants for drug delivery," *Encyclopedia of Biomaterials and Biomedical Engineering. 2nd ed. New York: Informa Healthcare, USA, Inc*, pp. 2259–2269, 2008.

(52) S.-Y. Lee and S.-P. Chee, "Surodex after phacoemulsification," *Journal of Cataract & Refractive Surgery*, vol. 31, no. 8, pp. 1479–1480, 2005.

(53) S. Mansoor, B. D. Kuppermann, and M. C. Kenney, "Intraocular sustained-release delivery systems for triamcinolone acetonide," *Pharmaceutical research*, vol. 26, no. 4, pp. 770-784, 2009.

(54) S.K. Seah *et al.*, "Use of surodex in phacotrabeculectomy surgery," *American journal of ophthalmology*, vol. 139, no. 5, pp. 927–928, 2005.

(55) D. T. Tan, S.-P. Chee, L. Lim, J. Theng, and M. Van Ede, "Randomized clinical trial of surodex steroid drug delivery system for cataract surgery: Anterior versus posterior placement of two surodex in the eye1 1The authors do not have a financial interest in this or competing products.," *Ophthalmology*, vol. 108, no. 12, pp. 2172–2181, 2001.

(56) D. T. Tan, S.-P. Chee, L. Lim, and A. S. Lim, "Randomized clinical trial of a new dexamethasone delivery system (Surodex) for treatment of post-cataract surgery inflammation," *Ophthalmology*, vol. 106, no. 2, pp. 223–231, 1999.

(57) J. A. Haller, P. Dugel, D. V. Weinberg, C. Chou, and S. M. Whitcup, "Evaluation of the safety and performance of an applicator for a novel intravitreal dexamethasone drug delivery system for the treatment of macular edema," *Retina*, vol. 29, no. 1, pp. 46–51, 2009.

(58) B. D. Kuppermann *et al.*, "Randomized controlled study of an intravitreous dexamethasone drug delivery system in patients with persistent macular edema," *Archives of Ophthalmology*, vol. 125, no. 3, pp. 309–317, 2007.

(59) B.H. Koffler, L.-07-01 S. Group, and others, "Lacrisert®(hydroxypropyl cellulose ophthalmic insert) significantly improves symptoms of dry eye syndrome and patient quality of life," *Investigative Ophthalmology and Visual Science*, vol. 50, no. 13, pp. 4660-4660, 2009.

(60) M. Hu, G. Huang, F. Karasina, and V. G. Wong, "VerisomeTM, a Novel injectable, Sustained Release, Biodegradable, Intraocular Drug Delivery System and Triamcinolone Acetonide," *Invest. Ophthalmol. Vis. Sci.*, vol. 49, no. 13, pp. 5627–5627, May 2008.

(61) J. I. Lim, M. R. Wieland, A. Fung, D. Y. Hung, and V. Wong, "A phase 1 study evaluating the safety and evidence of efficacy of IBI-20089, a triamcinolone intravitreal injection formulated with the VerisomeTM drug delivery technology, in patients with cystoid macular edema," *Investigative Ophthalmology & Visual Science*, vol. 50, no. 13, pp. 5395–5395, 2009.

(62) N. Umeki *et al.*, "Preparation and evaluation of biodegradable films containing the potent osteogenic compound BFB0261 for localized delivery," *Int J Pharm*, vol. 404, no. 1–2, pp. 10–18, Feb. 2011.

(63) P. Rokkanen, "BIODEGRADABLE IMPLANTS IN FRACTURE FIXATION: EARLY RESULTS OF TREATMENT OF FRACTURES OF THE ANKLE," *The Lancet*, vol. 325, no. 8443, pp. 1422–1424, Jun. 1985.

(64) I. Akmaz, A. Kiral, O. Pehlivan, M. Mahirogullari, C. Solakoglu, and O. Rodop, "Biodegradable implants in the treatment of scaphoid nonunions," *Int Orthop*, vol. 28, no. 5, pp. 261-266, Oct. 2004.

(65) D. W. Isenbarger and J. R. Resar, "Drug-eluting versus third-generation bare metal stents: The US strategy," *International Journal of Cardiovascular Interventions*, vol. 7, no. 4, pp. 171–175, Jan. 2005.

(66) G. Nakazawa, A. V. Finn, F. D. Kolodgie, and R. Virmani, "A review of current devices and a look at new technology: drug-eluting stents," *Expert review of medical devices*, vol. 6, no. 1, pp. 33–42, 2009.

(67) Y. Onuma and P. W. Serruys, "Bioresorbable Scaffold The Advent of a New Era in Percutaneous Coronary and Peripheral Revascularization?," *Circulation*, vol. 123, no. 7, pp. 779–797, Feb. 2011.

(68) J. A. Ormiston and P. W. S. Serruys, "Bioabsorbable Coronary Stents," *Circ Cardiovasc Interv*, vol. 2, no. 3, pp. 255–260, Jun. 2009.

(69) Y. B. Pride and D. E. Cutlip, "Disappearing stents—DREAMS of a sorcerer's apprentice?," *The Lancet*, vol. 381, no. 9869, pp. 787–789, Mar. 2013.

(70) Y. Wang, "Bioabsorbable stent with layers having different degradation rates," US8377533 B2, 19-Feb-2013.

(71) Y. Wang, "Implantable medical devices fabricated from polyurethanes with biodegradable hard and soft blocks and blends thereof," WO2009091661 A2, 23-Jul-2009.

(72) Y. Wang, D. A. Castro, and S. D. Pacetti, "Methods to improve adhesion of polymer coatings over stents," US8486482 B2, 16-Jul-2013.

(73) Y. Wang, D.C. Gale, and B. Huang, "Implantable medical devices fabricated from polymer blends with star-block copolymers," US8262723 B2, 11-Sep-2012.

(74) S.F.A. Hossainy, R. Rapoza, J. P. Oberhauser, and Y. Wang, "Bioabsorbable Stent and Treatment That Elicits Time-Varying Host-Material Response," US20100198330 A1, 05-Aug-2010.

(75) J. Oberhauser, S. Hossainy, and R. Rapoza, "Design principles and performance of bioresorbable polymeric coronary scaffolds," *EuroIntervention*, vol. 5, no. F, pp. F15–F22, Dec. 2009.

(76) A. Colombo and A. S. Sharp, "The bioabsorbable stent as a virtual prosthesis," *The Lancet*, vol. 373, no. 9667, pp. 869–870, Mar. 2009.

(77) B. D. Gogas, V. Farooq, Y. Onuma, and P. W. Serruys, "The ABSORB bioresorbable vascular scaffold: an evolution or revolution in interventional cardiology?," *Hellenic J Cardiol*, vol. 53, no. 4, pp. 301–309, Aug. 2012.

(78) A. LAFONT and E. DURAND, "ART: concept of a bioresorbable stent without drug elution," *EuroIntervention*, vol. 5, 2009.

(79) E. Durand *et al.*, "Adjusting a polymer formulation for an optimal bioresorbable stent: a 6-month follow-up study.," *EuroIntervention: journal of EuroPCR in collaboration with the Working Group on Interventional Cardiology of the European Society of Cardiology*, vol. 8, no. 2, pp. 242–249, 2012.

(80) J. Ziegler, U. Mayr-Wohlfart, S. Kessler, D. Breitig, and K.-P. Günther, "Adsorption and release properties of growth factors from biodegradable implants," *J. Biomed. Mater. Res.*, vol. 59, no. 3, pp. 422–428, Mar. 2002.

(81) O. Böstman, U. Päivärinta, E. Partio, J. Vasenius, M. Manninen, and P. Rokkanen, "Degradation and tissue replacement of an absorbable polyglycolide screw in the fixation of rabbit femoral osteotomies," *J Bone Joint Surg Am*, vol. 74, no. 7, pp. 1021-1031, Aug. 1992.

(82) T.C. Laurent and J. R. Fraser, "Hyaluronan," *FASEB J.*, vol. 6, no. 7, pp. 2397-2404, Apr. 1992.

(83) M. Kurisawa, J. E. Chung, Y. Y. Yang, S. J. Gao, and H. Uyama, "Injectable biodegradable hydrogels composed of hyaluronic acid–tyramine conjugates for drug delivery and tissue engineering," *Chem. Commun.*, no. 34, pp. 4312–4314, Aug. 2005.

(84) B. Jeong, Y. H. Bae, D. S. Lee, and S. W. Kim, "Biodegradable block copolymers as injectable drug-delivery systems," *Nature*, vol. 388, no. 6645, pp. 860–862, Aug. 1997.

(85) B. Ronneberger, W. J. Kao, J. M. Anderson, and T. Kissel, "In vivo biocompatibility study of ABA triblock copolymers consisting of poly(L-lactic-co-glycolic acid) A blocks attached to central poly(oxyethylene) B blocks," *J. Biomed. Mater. Res.*, vol. 30, no. 1, pp. 31–40, Jan. 1996.

(86) K.J. Zhu, L. Xiangzhou, and Y. Shilin, "Preparation, characterization, and properties of polylactide (PLA)–poly (ethylene glycol) (PEG) copolymers: A potential drug carrier," *J. Appl. Polym. Sci.*, vol. 39, no. 1, pp. 1–9, Jan. 1990.

(87) A. Chenite *et al.*, "Novel injectable neutral solutions of chitosan form biodegradable gels in situ," *Biomaterials*,

vol. 21, no. 21, pp. 2155–2161, Nov. 2000.

(88) C. Gebelein, *Applied Bioactive Polymeric Materials*. Springer Science and Business Media, 2013.

(89) K. Y. Lee, W. S. Ha, and W. H. Park, "Blood compatibility and biodegradability of partially N-acylated chitosan derivatives," *Biomaterials*, vol. 16, no. 16, pp. 1211–1216, Nov. 1995.

(90) S. Hirano, H. Tsuchida, and N. Nagao, "N-acetylation in chitosan and the rate of its enzymic hydrolysis," *Biomaterials*, vol. 10, no. 8, pp. 574–576, Oct. 1989.

(91) K. Sakai, R. Katsumi, A. Isobe, and F. Nanjo, "Purification and hydrolytic action of a chitosanase from Nocardia orientalis," *Biochim. Biophys. Acta*, vol. 1079, no. 1, pp. 65–72, Aug. 1991.

(92) O. Felt-Baeyens *et al.*, "Biodegradable scleral implants as new triamcinolone acetonide delivery systems," *Int J Pharm*, vol. 322, no. 1–2, pp. 6–12, Sep. 2006.

(93) J. A. Hubbell, C. P. Pathak, A. S. Sawhney, N. P. Desai, and J. L. Hill, *Photopolymerizable biodegradable hydrogels as tissue contacting materials and controlled-release carriers*. Google Patents, 1997.

(94) M. G. Fleming and W. A. Maillet, "Photopolymerization of composite resin using the argon laser," *J Can Dent Assoc*, vol. 65, no. 8, pp. 447–450, Sep. 1999.

(95) A. Hatefi and B. Amsden, "Biodegradable injectable in situ forming drug delivery systems," *Journal of Controlled Release*, vol. 80, no. 1–3, pp. 9–28, Apr. 2002.

(96) J.S. Temenoff and A. G. Mikos, "Injectable biodegradable materials for orthopedic tissue engineering," *Biomaterials*, vol. 21, no. 23, pp. 2405–2412, Dec. 2000.

(97) S. He, M. J. Yaszemski, A. W. Yasko, P. S. Engel, and A. G. Mikos, "Injectable biodegradable polymer composites based on poly(propylene fumarate) crosslinked with poly(ethylene glycol)-dimethacrylate," *Biomaterials*, vol. 21, no. 23, pp. 2389–2394, Dec. 2000.

(98) L.J. Suggs and A. G. Mikos, "Development of poly(propylene fumarate-co-ethylene glycol) as an injectable carrier for endothelial cells," *Cell Transplant*, vol. 8, no. 4, pp. 345–350, Aug. 1999.

(99) S. Lu and K. S. Anseth, "Photopolymerization of multilaminated poly (HEMA) hydrogels for controlled release," *J Control Release*, vol. 57, no. 3, pp. 291–300, Feb. 1999.

(100) H. Cui and P. B. Messersmith, "Thermally Triggered Gelation of Alginate for Controlled Release," in *Tailored Polymeric Materials for Controlled Delivery Systems*, vol. 709, 0 vols., American Chemical Society, 1998, pp. 203–211.

(101) S. Cohen, E. Lobel, A. Trevgoda, and Y. Peled, "A novel in situ-forming ophthalmic drug delivery system from alginates undergoing gelation in the eye," *Journal of Controlled Release*, vol. 44, no. 2–3, pp. 201–208, Feb. 1997.

(102) A. B. Lansdown and M. J. Payne, "An evaluation of the local reaction and biodegradation of calcium sodium alginate (Kaltostat) following subcutaneous implantation in the rat," *J R Coll Surg Edinb*, vol. 39, no. 5, pp. 284–288, Oct. 1994.

(103) Y. Suzuki *et al.*, "Evaluation of a novel alginate gel dressing: cytotoxicity to fibroblasts in vitro and foreign-body reaction in pig skin in vivo," *J. Biomed. Mater. Res.*, vol. 39, no. 2, pp. 317–322, Feb. 1998.

(104) A. Perry and R. E. Schmidt, "Cancer therapy-associated CNS neuropathology: an update and review of the literature," *Acta Neuropathol*, vol. 111, no. 3, pp. 197–212, Feb. 2006.

(105) J. Weingart *et al.*, "Phase I Trial of Polifeprosan 20 With *Carmustine* Implant Plus Continuous Infusion of Intravenous O6-Benzylguanine in Adults With Recurrent Malignant Glioma: New Approaches to Brain Tumor Therapy CNS Consortium Trial," *JCO*, vol. 25, no. 4, pp. 399–404, Feb. 2007.

(106) R. Erbel *et al.*, "Temporary scaffolding of coronary arteries with bioabsorbable magnesium stents: a prospective, non-randomised multicentre trial," *The Lancet*, vol. 369, no. 9576, pp. 1869–1875, 2007.

(107) E. Grube, "Bioabsorbable stent. The Boston scientific and REVA technology," *EuroPCR. May*, pp. 19–22, 2009.

(108) R. Kontio, R. Suuronen, O. Salonen, P. Paukku, Y. T. Konttinen, and C. Lindqvist, "Effectiveness of operative treatment of internal orbital wall fracture

with polydioxanone implant," *International journal of oral and maxillofacial surgery*, vol. 30, no. 4, pp. 278–285, 2001.

(109) A.P. Pego *et al.*, "In vivo behavior of poly (1, 3-trimethylene carbonate) and copolymers of 1, 3-trimethylene carbonate with D, L-lactide or ϵ-caprolactone: Degradation and tissue response," *Journal of Biomedical Materials Research Part A*, vol. 67, no. 3, pp. 1044–1054, 2003.

(110) A. U. Daniels, K. P. Andriano, W. P. Smutz, M. K. Chang, and J. Heller, "Evaluation of absorbable poly (ortho esters) for use in surgical implants," *Journal of Applied Biomaterials*, vol. 5, no. 1, pp. 51–64, 1994.

(111) A. K. Walduck, J. P. Opdebeeck, H. E. Benson, and R. Prankerd, "Biodegradable implants for the delivery of veterinary vaccines: design, manufacture and antibody responses in sheep," *J Control Release*, vol. 51, no. 2–3, pp. 269–280, Feb. 1998.

(112) J. I. Lim, M. R. Wieland, A. Fung, D. Y. Hung, and V. Wong, "A Phase 1 Study Evaluating the Safety and Evidence of Efficacy of IBI-20089, A Triamcinolone Intravitreal Injection Formulated With the VerisomeTM Drug Delivery Technology, in Patients With Cystoid Macular Edema," *Invest. Ophthalmol. Vis. Sci.*, vol. 50, no. 13, pp. 5395–5395, Apr. 2009.

(113) D. F. Kiernan and W. F. Mieler, "The use of intraocular corticosteroids," 2009.

دراسة متمعنه في البوليمرات القابلة للتحلل البيولوجي المستخدمة في عمليات الغرس

رفيف مساعدة*، رنا عبيدات، معتصم الصمادي، بشار الطعاني، مي خنفر، روضة الشياب، محمد القاعود

قسم الصيدلة التكنولوجية، كلية الصيدلة، الجامعة العلوم والتكنولوجيا الأردنية

ملخص

إن نظام توصيل الدواء المغروس والقابل للتحلل البيولوجي (BIDDS) تم شرحه في هذه الورقة. كان اكتشاف البوليمرات القابلة للتحلل البيولوجي في مرحلة مبكرة من الستينات الخطوة الأولى لتطوير الغرسات القابلة للتحلل حتى المرحلة الحالية. إن مزايا الغرسات القابلة للتحلل الحيوي على الغرسات غير القابلة للتحلل البيولوجي تحفز العلماء على تطوير هذا البحث الميداني. تقدم هذه الورقة ملخصًا مفصلاً عن البوليمرات المستخدمة في أنظمة توصيل الدواء المزروعة القابلة للتحلل والتي تستخدم في الكثير من التطبيقات العلاجية والمجالات مثل علاج السرطان وعلاج الأمراض الوعائية ومعالجة العين وتسليم اللقاحات. كما أنه يصف تطوير الصيغ من أجل زيادة الكفاءة وامتثال المريض للشفاء والحد من الآثار الجانبية. كما تم ذكر تحديات ومستقبل أنظمة توصيل الدواء المزروعة القابلة للتحلل.

الكلمات الدالة: البوليمرات، عمليات الغرس، نظام تقديم الدواء.

تاريخ استلام البحث 2016/12/18 وتاريخ قبوله للنشر 2017/12/20.