A REVIEW ON: A BIOCOMPATIBLE POLYMERS AS LOCALIZED THERAPEUTICS

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ABSTRACT:

Polyanhydrides (PAs) are synthetic, biodegradable polymers designed for controlled drug delivery. They can be synthesized and scaled up from low-cost starting materials, and their structure can be tailored synthetically to achieve desired properties. PAs are biocompatible and biodegradable, and they break down into nontoxic metabolites that are easily eliminated from the body. A key feature of polyanhydrides is that water penetrates the PA matrix more slowly than the anhydride bonds cleave. This behavior makes PAs "surface-eroding drug delivery carriers," where degradation occurs layer-by-layer from the outside in. As a result, a variety of PA-based drug delivery systems have been developed, including solid implants, pasty injectable formulations, microspheres, and nanoparticles.

KEY WORDS: drug delivery, Gliadel, implants, localized carriers, polyanhydrides, Septacin, surface eroding polymers

1. INTRODUCTION:

The constant efforts of drug delivery scientists have been to maximize the therapeutic effect of the drug and minimize the adverse effects. Drugs given by conventional routes like oral, IV, IM injections are distributed to all body parts which include both, target and non-target sites. Systemic delivery exposes the entire body to the drug, even though the therapeutic effect is needed only at one specific site. Many old drugs, new pharmaceuticals, and new molecular entities can be reformulated for improved safety, efficacy, and even to create entirely new therapies.[1]. Many disease conditions like cancer (especially solid tumors) [2], thrombosis, restenosis [3], osteomyelitis [4], local infection [5], glaucoma and retinal disorders [6] are difficult to treat by systemic therapy. The complexity of these diseases and the serious consequences limit the systemic therapy. For example, Retinal diseases are difficult to treat with systemic drugs due to the blood-retinal barrier, risk of systemic toxicity, and potential hemorrhagic complications. when Systemic administration of antithrombotic agents and cancer drugs for localized diseases leads to whole-body exposure and serious side effects.[7]. Polymer delivery is one of the simplest strategies for site-specific drug targeting. Polymers are widely used in therapeutics, and their localized use is especially important. For local applications, polymers can act in 3 ways:

1. Structural – provide support/framework

2. Functional – improve biocompatibility or control drug release

3. Both – combine structural support with drug delivery functions

Functionally active polymers specifically enhance biocompatibility and help medical devices work better while delivering drugs and the operation of a medical device or to deliver the pharmacologically active agents [8]. the advantages of using polymers should be weighed against following concerns: (1) the toxicity of polymers and their degradation products in the body i.e. biocompatibility (2) the overall cost of polymeric drug delivery systems

(3) problems associated with release, i.e. Other limitations include dose dumping or release failure, and discomfort from the delivery system itself or its insertion method.[9].

1.1 TYPES

For drug delivery, polymers are broadly divided into non-biodegradable and biodegradable systems [10]. Biodegradable polymers are preferred because they self-eliminate after drug release, eliminating the need for surgical removal of the implant. Their wide clinical acceptance comes from their tunability: biodegradation rates can be precisely controlled by incorporating different labile chemical groups into the polymer backbone. Biodegradable polymers break down and are eliminated by the body on their own. No surgery needed to remove the implant after the drug is delivered. They're widely accepted because their degradation rate can be controlled by adding different "labile groups" — chemical bonds that break easily. This lets you tune the breakdown rate to match the drug release you need. In short: Self-eliminating + tunable degradation = no removal surgery and customizable drug release timing. Biodegradation can be enzymatic, chemical, or of microbial origin or simply by hydrolysis [11].

2. LOCALIZED DRUG DELIVERY: BIOPHARMACEUTICAL AND PHARMACOKINETIC ADVANTAGES

Even with high-throughput and ultrahigh-throughput screening, discovering new drugs remains slow, difficult, and costly compared to developing better drug delivery systems. Because of this, the field has shifted focus: instead of only hunting new drugs, scientists now work on delivering existing drugs more efficiently. The aim is to give old drugs a "new life" by boosting therapeutic effects and cutting adverse effects through smarter delivery.

Drug discovery moved from slow, traditional methods to HTS and UHTS to find new targets/drugs. Despite tech advances, developing new drugs is still tedious, slow, and extremely expensive compared to improving delivery systems. Focus is moving toward delivering existing drugs more efficiently instead of just making new ones. Give old molecules a "new life" by maximizing therapeutic benefit and minimizing side effects through better delivery. It's often faster and cheaper to fix how we deliver old drugs than to invent brand new ones.

2.1 BENEFITS OF LOCALIZED DELIVERY FOR PROBLEM DRUGS

Localized drug delivery offers many advantages with the main improvement being in high locoregional concentration of therapeutic agent/s with prolonged retention (especially for drugs with high extraction ratio) [12]. Prolonged release can be achieved in two ways, either by preventing drug efflux from the site or by using delivery vehicles that will prolong the duration of release [13].

1.LOW/VARIABLE BIOAVAILABILITY

Drugs that are poorly absorbed or vary a lot between patients can still be delivered successfully with localized systems. This is critical for drugs with a *narrow therapeutic index*, were small dose changes cause toxicity or treatment failure.

2. DOSE-DEPENDENT ACTIVITY

For drugs where effects depend on concentration, local delivery cuts side effects at non-target sites while keeping full therapeutic benefit at the site of action. Localized delivery fixes bioavailability issues and separates therapeutic effects from systemic side effects, making risky or inconsistent drugs safer and more reliable

The target region requires less of the drug to fill the local volume of distribution and hence the chances of adverse effects are reduced or completely eliminated due to the reduction of systemic dose to achieve the same drug concentration at the diseased tissue site [14,15]. Proliferating biotech drugs have a relatively short half-life, specifically proteins and peptides, and others such as nucleic acids and oligonucleotide can also be delivered locally with minimal loss of therapeutic activity during the transit time to reach the site of action [16]. Moreover, low bioavailable drugs and drugs with variable bioavailability (varied inter-individual pharmacokinetic) can also be delivered successfully; this is particularly important for narrow therapeutic index drugs.

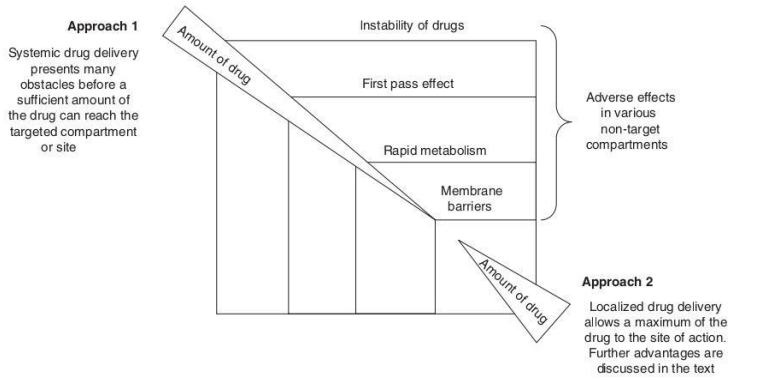

Figure 1. Schematic diagram representing advantage of localized drug delivery over systemic delivery. More efficiently use of drug in former case in terms of barriers to overcome and minimal/no adverse effects.

2.2 CHALLENGE OF ANTICANCER DRUG DELIVERY

Tumors often have poor blood supply after radiation or surgery, so anticancer drugs delivered systemically can't reach the tumor effectively. Anticancer drugs are toxic to other organs, so patients usually need pre-medication or simultaneous drugs to manage those side effects [17]. Direct tumoral delivery bypasses the blood supply issue and reduces damage to healthy organs, since the drug stays mostly at the tumor site

ADVANTAGES OF POLYANHYDRIDES (PAS) IN DRUG DELIVERY

1. **CONTROLLED EXPOSURE:** PAs degrade heterogeneously from the surface, so the drug stays protected and isn't exposed until the polymer starts breaking down at the target site.

2. **SOL-GEL PAS-INJECTABLES:** Newer polyanhydrides with sol-gel properties can be injected as a liquid and solidify in the body.

BENEFIT: No surgery needed to implant the delivery system — you just inject it directly at the affected site.

2.3 CHOICE OF POLYMER FOR LOCALIZED DRUG DELIVERY: POLYANHYDRIDES

It is necessary to develop rational approaches for creating improved biomaterials for drug delivery, especially biodegradable polymers. Any polymer that is used as drug carrier should have the following properties of:

- Biocompatibility: Safe for implantation in the target organ without causing adverse tissue reactions;
- Being eliminated completely from the implantation site in predictable time;
- Being easy to manufacture at a reasonable cost [18,19].
- Having suitable physical properties for the device fabrication (low melting point, usually below 100 degrees, and soluble in common organic solvents)

Most of the above criteria can be fulfilled by many natural polymers, for example collagen, albumin, polyglutamic acid, etc., as well as synthetic polymers, for example polyesters, PAs, polyorthoesters, biodegradable polymers. Natural polymers are amply available, but they have limited use because of batch-to-batch variability, difficulty in processing and the potential risk of transmitting animal-originated pathogens and immunogenicity [20,21]. Synthetic polymers, in contrast, can be produced in a reproducible manner with better quality control. Natural polymers are amply available, but they have limited use because of batch-to-batch variability, difficulty in processing and the potential risk of transmitting animal-originated pathogens and immunogenicity [22,23]. Synthetic polymers, in contrast, can be produced in a reproducible manner with better quality control. Among synthetic polymers, the choice is dictated by the desired degradation/erosion pattern. Degradation and erosion are used synonymously but in fact degradation of the polymer designates the process of polymer chain cleavage [24] while erosion is the sum of all processes that lead to the loss of mass from a polymer matrix [25]. Erosion of the polymer matrices depends on processes such as rate of degradation, swelling, porosity and ease of diffusion of oligomers and monomers from the matrices. The decrease in the device thickness throughout the erosion process, maintenance of the structural integrity and nearly zero-order degradation kinetics suggest that heterogenous surface erosion predominates in PAs [26,27]. By varying the type of monomer and their ratios in PA-based copolymers, surface eroding polymers with a degradation time from one week to several years can be designed and synthesized. The hydrolytic degradation rates can be varied several thousand folds by simple changes in the polymer backbone and by altering the hydrophobic and hydrophilic balance of the polymer [28,29].

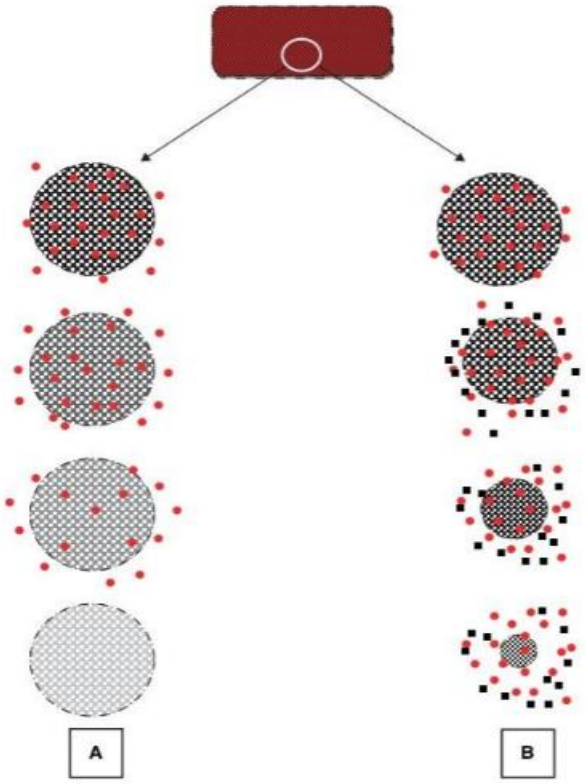

Figure 2. Depiction of drug release and polymer degradation from a polymeric drug delivery system. Black squares and red circles represent the polymer matrix and drug, respectively. (**A**) is homogeneous/bulk erosion where drug release occurs without polymer mass loss, which occurs slowly and continues even after drug release is complete, whereas in (**B**) heterogeneous/surface erosion, both the processes occur simultaneously and polymer erosion is completed as soon as drug release is complete.
Please see online version of the article for the colour figure.

3. DEGRADATION OF POLYANHYDRIDES

Polymer degradation is critical in material selection because it determines the drug delivery system's lifetime and overall fate, its disposition in the body, storage conditions, and drug release kinetics.

Degradation drives selection: How a polymer breaks down determines the delivery system's lifespan, how it's cleared from the body, storage needs, and drug release rate.

PAs chemistry = fast surface erosion: Polyanhydrides are built from hydrophobic monomers linked by highly water-sensitive anhydride bonds.

These hydro-labile bonds cause rapid degradation at the device surface while the core stays intact. This surface erosion gives predictable, controlled drug release right at the target site. That combo of hydrophobic backbone + fast surface breakdown makes PAs one of the best polymer classes for localized drug delivery. Chemically, polyanhydrides are made of hydrophobic monomers connected by highly hydro-labile anhydride bonds. These bonds drive rapid degradation at the device surface, which is why PAs are considered one of the most suitable polymer classes for localized drug delivery. The pH of the surrounding medium strongly influences degradation through a two-part effect: first, the hydrolysis reaction is base-catalyzed, and second, higher pH increases the

solubility of the acidic degradation products, helping move them away from the eroding matrix [30.] Although PAs degrade by surface erosion, many factors influence both the mechanism and the rate of degradation, such as the type of monomers used and their composition. As with most polymers, amorphous regions erode faster than crystalline ones, and PAs follow the same trend. All-aliphatic PAs tend to be rigid, crystalline materials whose melting point increases with monomer chain length [31]. However, their very fast degradation rates limit pharmaceutical use, with some exceptions like P(FA:SA), which has useful bio-adhesive properties. In contrast, aromatic PAs are high-melting polymers that degrade very slowly. To balance these properties, aliphatic and aromatic PAs have been copolymerized to produce materials with improved mechanical characteristics and tunable erosion times [32,33]. The most prominent example is P(CPP:SA), used in Gliadel, which has been reported to release drug via a surface erosion mechanism [34,35]. In P(CPP:SA), the erosion zones are highly porous and are separated from the non-eroded polymer by distinct erosion fronts. These fronts move at a constant velocity from the surface of the matrix toward its center, which is consistent with true surface erosion behavior [36]. Fatty acid–based polymers represent an important class of polyanhydrides, and P(FAD:SA) is one of the most extensively studied copolymers in this group. P(FAD:SA) also shows an erosion zone, but due to the very low solubility of FAD, the zone does not form a porous structure. Instead, it consists mainly of a semisolid mixture of FAD and FAD salts. This difference in erosion zone morphology explains why FAD-rich systems deviate from ideal zero-order release, since the insoluble residue hinders both water access and drug diffusion.

. Normal PAs = hydrophobic monomers + water-sensitive anhydride bonds. When water hits the implant, the anhydride bonds at the surface breaks fast. The degraded monomers dissolve away, leaving a porous erosion zone behind. surface reacts, core stays solid, and water/drugs can move freely through the pores that form [37]. That gives predictable, zero-order drug release. This how the erosion behavior of the fatty acid-based polymer. P(FAD:SA) = poly (fatty acid dimer: sebacic acid). FAD is a large, waxy fatty acid dimer. It's extremely hydrophobic and has very low water solubility. So, when the anhydride bonds break, SA dissolves and leaves. But FAD doesn't. It just turns into FAD + FAD salts that stay behind as a semisolid, greasy layer [38]. The semisolid layer that forms in FAD-containing systems acts as a permeation barrier, and sebacic acid has been found to precipitate inside the erosion zone. This ultimately slows the release of both SA and the incorporated drug, disrupting the ideal surface-erosion kinetics. Ricinoleic acid–based polyanhydrides show a different degradation profile. In vitro, they undergo a sharp drop in molecular weight within the first 24 hours of erosion and lose about 40% of their anhydride bonds within 48 hours [39]. For poly(ester-anhydride) s made from ricinoleic acid and sebacic acid, degradation proceeds in two distinct stages. In the first stage, lasting about one week, the anhydride bonds are completely hydrolyzed. This releases the SA units that were conjugated at both carboxylic acids via anhydride linkages. In the second stage, the remaining RA–RA or RA–SA oligoesters break down further into shorter RA ester dimers, trimers, and tetramers, as well as RA–SA dimers. For poly(ester-anhydride)s made from ricinoleic acid and sebacic acid, degradation occurs in two distinct stages. In the first stage, which lasts about one week, the anhydride bonds are completely hydrolyzed. This releases the sebacic acid units that were conjugated at both carboxylic acids via anhydride linkages. In the second stage, the remaining RA–RA or RA–SA oligoesters break down further into shorter RA ester dimers, trimers, and tetramers, as well as RA–SA dimers. These smaller fragments then dissolve in the aqueous degradation medium [40]. In contrast, fatty acid–based systems like P(FAD:SA) behave differently due to the very low solubility of FAD. Instead of forming a porous erosion zone, they develop a semisolid layer composed mainly of FAD and FAD salts. This semisolid layer acts as a permeation barrier, and sebacic acid has been observed to precipitate inside the erosion zone. The result is slowed release of both SA and the incorporated drug, which undermines the zero-order kinetics expected from surface erosion.

The general problem for these polymers is usually, that this semisolid layer acts as a permeation barrier. Sebacic acid (SA) also precipitates inside the erosion zone. Because that semisolid FAD layer blocks diffusion, it becomes a permeation barrier. Sebacic acid can't get out, so it builds up and precipitates inside the zone.

3.1 KEY POINTS ON POLYANHYDRIDE DEGRADATION

KEY MECHANISM: Surface erosion happens because water only penetrates the outer layer to hydrolyze anhydride bonds. The hydrophobic matrix blocks bulk water entry.

3.1.1. WHY SURFACE EROSION HAPPENS

Surface erosion occurs because water must penetrate the matrix to hydrolyze anhydride bonds. Polyanhydrides are hydrophobic, so water can't soak the bulk – hydrolysis is limited to the surface. As the surface hydrolyzes, the matrix breaks into degradation products.

3.1.2. PSADT IN VITRO STUDY SETUP

- **Material:** Poly(sebacic acid), Di acetoxy terminated = PSADT

- **Form:** Circular tablets made by compression molding

-**Method:** Immersed in PBS. Degradation tracked by molecular weight loss + mass loss. SEM used to watch surface morphology over time.

3.1.3. IN VIVO VS IN VITRO LINK

The dependence of elimination rate on monomer solubility held up both in vitro and in vivo. So PBS tests are a reasonable predictor of body behavior for PAs.

3.1.4. BIOCOMPATIBILITY CONCLUSION

All polymers tested were biocompatible and suitable as drug carriers.

This study reinforces that PAs degrade by surface erosion, give near zero-order release, and their lifetime is tunable by monomer choice + device geometry. The Achilles' heel is monomer solubility – go too hydrophobic and you lose the fast, predictable erosion.

3.1. 5. PSADT DATA SHOWED:

elimination time depends on monomer solubility. That's the same rule here.

x = 4–8: soluble monomers → 7-14 days erosion → clean surface erosion.

x = 10–12: low solubility → 8+ weeks → semisolid barrier formation

FAD is x = 36. It's an extreme case of that "low solubility" group.

Polyanhydrides are picked for surface erosion, but only if the degradation products can leave. FAD violates that assumption. You get a system that erodes chemically but releases drug physically, and the two rates no longer match. That's why FAD:SA ratios are kept low, or FAD is blended with PEG to increase hydrophilicity.

3.1.6. MAIN EXPERIMENTAL FINDINGS

(1). Zero-order kinetics → Confirmed surface erosion. Mass loss was linear with time, not exponential like bulk erosion.

(2). Geometry matters: Tablet shape/size changed the surface-area-to-volume ratio, which directly controlled degradation rate. Thinner or higher surface area = faster erosion.

(3). Processing temperature didn't matter: Molding temp had no significant effect on degradation rate. Means the polymer is thermally stable during processing.

(4). Monomer solubility controls elimination time:

- **Soluble monomers** (x = 4–8 carbons): Cleared in 7–14 days in vivo and in vitro.

- **Low solubility monomers** (x = 10–12 carbons): Took ~8 weeks to eliminate. Matches your earlier FAD problem – insoluble products stall erosion.

(5). Enzymes don't speed it up: Common hydrolytic enzymes around implants had no effect. Degradation is purely chemical hydrolysis, not enzymatic.

3. The problem this creates

Normal PA erosion zone	P(FAD:SA) erosion zone
Porous, water-filled	Semisolid, waxy FAD/FAD salts
Water and drug diffuse out easily	Semisolid layer acts like a plug
SA dissolves and exits	SA precipitates inside the waxy layer

3.2 IN VIVO DEGRADATION AND ELIMINATION OF POLYANHYDRIDES

Polyanhydrides are composed of sparingly water-soluble diacid monomers linked by anhydride bonds. These anhydride bonds are extremely hydro-labile and split rapidly into two carboxylic acids when exposed to water. The hydrolysis reaction is base-catalyzed. The degradation rate in vivo is controlled by two main factors. First, the pH of the surroundings — higher pH accelerates base-catalyzed hydrolysis. Second, the solubility of the degradation products. If the resulting diacids or oligomers do not dissolve well, they accumulate at the surface. That buildup slows further breakdown and can hinder drug diffusion.

The primary mechanism of degradation in vivo is hydrolysis, which breaks the polymer down into non-toxic diacid monomers. These monomers are then metabolized or excreted through normal physiological pathways. Because the polyanhydride backbone is hydrophobic, water penetration into the bulk is limited. This forces surface erosion rather than bulk erosion.

This surface erosion behavior is critical for drug delivery. The polymer erodes layer-by-layer from the outside in, so the drug release rate directly tracks the polymer erosion rate. That gives predictable, sustained, localized

delivery. This property is why polyanhydrides are used in products like Gliadel wafers for brain tumor chemotherapy. The combination of unstable anhydride bonds and hydrophobic monomers produces fast surface hydrolysis, safe breakdown products, and controlled release that is ideal for local therapy.

3.2.1 WHY POLYANHYDRIDE PROPERTIES MATTER FOR DRUG DELIVERY

Surface erosion leads to predictable release. The hydrophobic backbone keeps water out of the bulk, so only the surface hydrolyzes and the implant erodes layer-by-layer. The result is near zero-order, constant drug release without the burst or dump effects seen with PLGA. Gliadel wafers, for example, provide about three weeks of steady chemotherapy in the brain. Degradation is also highly tunable. Anhydride hydrolysis is base-catalyzed and depends on monomer solubility. Choosing different monomers or ratios changes the lifetime: sebacic acid–based PAs degrade in days to weeks, CPP-based ones last months, and fatty acid dimer–based ones can last months to years. PAs are also stable during storage but degrade at body pH. The catch is that if monomers like FAD are too insoluble, they form a waxy barrier that traps drug and sebacic acid, ruining the surface-erosion benefit.

Finally, PAs form safe, disappearing implants. They break down into non-toxic diacids such as sebacic acid that are metabolized or excreted. There is no acid burst or inflammation like with some other biodegradable polymers. If monomers like FAD are too insoluble, they form a waxy barrier that traps drug/SA and ruins the surface-erosion benefit.

3.3 IN VITRO DEGRADATION: KEY FINDINGS FROM PSADT STUDIES

Surface erosion occurs because water must penetrate the matrix to hydrolyze anhydride bonds. Polyanhydrides are hydrophobic, so water cannot soak the bulk — hydrolysis is limited to the surface. As the surface hydrolyzes, the matrix breaks into degradation products. This was demonstrated in vitro using poly(sebacic acid), Di acetoxy terminated, or PSADT. Circular tablets were made by compression molding and immersed in PBS. Degradation was tracked by molecular weight loss and mass loss, and SEM was used to observe surface morphology over time. Several key findings emerged. Mass loss was linear with time, confirming zero-order kinetics and true surface erosion rather than exponential bulk erosion. Device geometry mattered significantly: tablet shape and size changed the surface-area-to-volume ratio, which directly controlled the degradation rate. Thinner parts or higher surface area led to faster erosion. Processing temperature had no significant effect on degradation rate, indicating the polymer is thermally stable during manufacturing.

Monomer solubility was shown to control elimination time. Soluble monomers with 4–8 carbons were cleared in 7–14 days both in vitro and in vivo. Low solubility monomers with 10–12 carbons took about 8 weeks to eliminate. This matches the known problem with FAD, where insoluble products stall erosion. Enzymes did not speed up degradation — common hydrolytic enzymes found around implants had no effect, confirming that degradation is purely chemical hydrolysis, not enzymatic. The dependence of elimination rate on monomer solubility held up both in vitro and in vivo, so PBS tests are a reasonable predictor of body behavior for PAs. All polymers tested were biocompatible and suitable as drug carriers.

3.3.1 THE CORE DESIGN RULE: MONOMER SOLUBILITY GOVERNS PERFORMANCE

This work reinforces that PAs degrade by surface erosion, give near zero-order release, and their lifetime is tunable by monomer choice and device geometry. The major limitation is monomer solubility. If you go too hydrophobic, you lose the fast, predictable erosion.

PSADT data illustrated the same rule: monomers with 4–8 carbons give 7–14 days erosion and clean surface erosion, while those with 10–12 carbons give 8+ weeks and form semisolid barriers. FAD, at 36 carbons, is an

extreme case of the "low solubility" group. Polyanhydrides are chosen for surface erosion, but that only works if the degradation products can leave. FAD violates that assumption. The system still erodes chemically, but drug release becomes a physical diffusion process out of a waxy FAD residue. The two rates no longer match. For that reason, FAD:SA ratios are kept low in formulations, or FAD is blended with PEG to increase hydrophilicity.

The FAD layer creates 3 issues:

Problem	Mechanism	Consequence
Diffusion barrier	Semisolid FAD blocks water from reaching fresh polymer	Hydrolysis slows down. Erosion rate drops below prediction
Drug trapping	Drug must diffuse through waxy FAD layer	Release becomes diffusion-controlled, not erosion-controlled. No longer zero-order
SA precipitation	SA can't exit fast enough, builds up in FAD layer	SA crashes out as solid inside the zone, further blocking pores

So instead of `erosion rate = drug release rate`, you get `drug release rate = diffusion through FAD sludge`. That's slow, variable, and depends on how the semisolid layer cracks or emulsifies.

3.4INVITRO DEGRADATION OF POLYANHYDRIDES

3.4.1. SURFACE EROSION MECHANISM: Water must diffuse into the matrix and hydrolyze anhydride bonds. Hydrophobic PAs limit water to the surface, so only the outer layer breaks down. Then the matrix collapses into monomer degradation products**.**

3.4.2. EXPERIMENTAL DESIGN – PSADT

Polymer: PSADT = poly(sebacic acid), Di acetoxy terminated. Sebacic acid = C10 diacid, so x = 8 in your monomer series.

Fabrication: Compression molded into circular tablets → controls geometry, avoids solvents. In vitro test: Tablets in PBS at 37°C. PBS mimics pH and ionic strength of body fluids.

In vitro test: Tablets in PBS at 37°C. PBS mimics pH and ionic strength of body fluids.

3.4.3CONSIDERATIONS FOR THEIR MEASUREMENTS:

- Molecular weight drop → bond cleavage rate
- Mass loss → overall erosion rate
- Anhydride bond content → chemistry of degradation
- Monomer release → what's actually leaving the tablet
- SEM → visual proof of surface erosion vs bulk pitting

IN VITRO VS IN VIVO AGREEMENT

The same monomer solubility rule held in animals and in PBS. That's huge: means you can screen new PA chemistries in the lab and trust the elimination time will scale to humans. x = 8 sebacic acid is "soluble enough" → 7–14 days clearance. That's why Gliadel uses CPP:SA – SA gives the fast erosion component.

WHY PSADT SPECIFICALLY SHOWED SURFACE EROSION

- **Hydrophobic backbone:** SA is C10, so the polymer hates water. Bulk stays dry.
- **Soluble monomer:** SA dissolves fast once cleaved. No buildup, no barrier. Pores stay open.
- **No autocatalysis:** Unlike PLGA, SA is a weak acid and washes away. No acid buildup inside to cause bulk degradation**.**

3.4.4KEY RESULTS AND THEIR MEANING

Finding	Data	Drug delivery implication
Near zero-order kinetics	Mass loss vs time was linear	Confirms surface erosion. Drug release would be constant, not burst. Ideal for 1–2 week therapy
Geometry controls rate	Thinner or higher SA:V tablets degraded faster	You can tune dose duration by changing shape, not just chemistry. A flat wafer erodes faster than a sphere
Processing temp irrelevant	Molding temp didn't change rate	Manufacturing is robust. No need to worry about thermal damage changing release
Monomer solubility = elimination time	x = 4–8 → 7–14 days; x = 10–12 → 8 weeks	Matches the FAD problem we discussed. If monomer can't dissolve, it plugs the erosion zone and slows everything
Enzymes do nothing	Hydrolytic enzymes didn't speed degradation	Erosion is purely chemical. More predictable than polymers that need enzymes, because enzyme levels vary patient-to-patient

4. HISTORY OF PAS

Polyanhydrides were first discovered in 1909 by Bucher and Slade [41]. At the time they were only a chemical curiosity with no practical application, and research on them remained largely dormant for decades. Interests resurfaced almost 50 years later when Conix explored aromatic polyanhydrides in the 1950s [42]. These versions were more hydrolytically stable than earlier aliphatic types and could be drawn into fibers for textile applications. Although this showed PAs had material utility, they were still not considered for medical use. Work on aliphatic polyanhydrides actually predates Conix. In the 1930s, Hill and Carothers [43] synthesized PAs from adipic and sebacic acid. However, their rapid hydrolytic instability was seen as a fatal flaw for plastics and fibers. Because

they degraded too quickly in the presence of water, development was abandoned. During the 1960s and 70s, Yoda and colleagues also developed heterocyclic polyanhydrides that had good film and fiber-forming properties, but again the focus was non-medical [44]. The major turning point came in the 1980s with Robert Langer and coworkers. They recognized that the same hydrolytic instability that doomed PAs as commodity plastics made them ideal for controlled drug delivery [45,46]. A polymer that falls apart predictably in water could be used as a temporary implant that releases drug as it erodes, then disappears. Once the degradable and biocompatible nature of PAs was established, Langer, Brem, Domb and others developed a wide range of copolymers specifically for medical use. This work led to clinical products like the Gliadel wafer, a P(CPP:SA) implant for brain cancer approved by the FDA in 1996.

In short, polyanhydrides went from an abandoned polymer in the 1930s to a drug delivery platform in the 1980s because the field changed what it considered a "problem." Water sensitivity was once the reason to drop them; later it became the reason to use them.

5.CLASSIFICATION OF PAS

Polyanhydrides can be broadly divided into homo-polyanhydrides and hetero-polyanhydrides. For erodible drug delivery materials, however, copolymers or hetero-polyanhydrides are far more important. Using copolymers allows us to tune erosion rates by changing the monomer type and ratio, which lets us hit different target release times.

Most PA copolymers use poly (sebacic acid), or PSA, as the aliphatic component. Because PSA is so common, these copolymers are usually classified by the other comonomer, since that part dictates the final polymer properties. The most studied example is the aromatic polyanhydride P(CPP:SA), which led to the FDA-approved Gliadel wafer [47,48]. Other aromatic PAs in this family include P(CPH:SA), P(CPM:SA), and P(CPV:SA).

There are also aliphatic-aromatic PA copolymers based on common diacids such as isophthalic acid (IPA), terephthalic acid (TA), and fumaric acid (FA) [49]. These copolymers are highly soluble in chloroform or dichloromethane, melt above 250 °C, and remain stable when stored at 25 °C. When fumaric acid is copolymerized with aliphatic diacids like sebacic acid, the resulting polymers are less crystalline and still soluble in chlorinated hydrocarbons [50]. Another major group for controlled drug release is fatty acid-based polyanhydrides. This class has been studied extensively and breaks into several subclasses. The first subclass covers linear and non-linear fatty acid terminated PAs. The second subclass is fatty acid dimer-based PAs, where most research has focused on erucic acid copolymers, though oleic acid and linoleic acid dimers have also been used with sebacic acid for drug delivery [51,52,53]. The third and newest subclass is ricinoleic acid-based PAs. Many of these have desirable properties for injectable, localized delivery, including low melting points, high hydrophobicity, and good polymer flexibility [54].

6. POLYANHYDRIDES IN CLINICAL PRACTICE

6.1 GLIADEL

Gliadel Wafer (carmustine implant) is a biodegradable chemotherapy implant used during brain surgery to treat malignant gliomas. It delivers medication directly to the tumor site, minimizing whole-body exposure.

6.1.1 ROLE IN LOCALIZED DRUG CARRIER SYSTEM

It has a core role in localized drug delivery which are as follows:

- **Direct Site-Targeting:** Up to 8 dime-sized wafers are implanted directly into the cavity walls and floor immediately after the surgeon removes the primary tumor. This directly targets residual, invisible cancer cells that commonly cause recurrence at the resection margin.
- **Controlled, Sustained Release:** The polymer matrix (a polyanhydride called Polifeprosan 20) gradually degrades in the presence of cerebrospinal fluid. As it breaks down, it releases the chemotherapeutic drug carmustine (BCNU) over approximately 5 to 7 days.
- **Bypassing Toxicity:** Systemic intravenous administration of carmustine can cause severe toxicities (like lung damage and bone marrow suppression). Local delivery circumvents this, allowing for significantly higher local drug concentrations**.**

Chemotherapy constitutes an important component in the cancer management, however access to the tumor site is limited by the blood-brain-barrier (BBB) and, moreover, most of the anticancer drugs are large, ionically charged or hydrophilic and thus are unable to cross the BBB; intolerably high systemic drug levels are required to achieve the therapeutic doses within the CNS. The localized therapy resolves the problem associated with the delivery of anticancer drugs, particularly in the case of the solid tumors. BCNU is a nitrosoureas, which despite having very short half-life, is considered as a 'gold standard' for treating brain tumor locally. Polyanhydride polymer matrix of poly[bis(p-carboxyphenoxy) propane with sebacic acid P(CPP:SA) (20:80 molecular ratio) is utilized for controlled delivery of BCNU in the form of Gliadel which is sterile, off-white to pale yellow wafer with a diameter of 1.45 cm and 1mm thickness. If BCNU is given systemically, its half-life is about 12 min, which forbids its use through conventional means. By contrast, when delivered by polymer, the concentration of BCNU was not only log orders higher in the brain than achievable by systemic administration, but the drug was also delivered over a period of 2-3 weeks and with minimal systemic toxicity. Brain tumors are one of the most devastating forms of disease, and their incidence demands serious attention. Rates are higher in more developed countries, with about 5.8 cases per 100,000 males and 4.1 per 100,000 females each year [55]. More than three-quarters of these primary brain tumors are malignant gliomas. A typical glioblastoma grows very rapidly, and by the time symptoms appear the tumor volume is already life-threatening [56]. Standard treatment for gliomas begins with biopsy for diagnosis, followed by surgical resection if the tumor can be removed without major brain damage. This is then followed by radiation and chemotherapy [57-60]. Despite improvements in neuroradiology and neurosurgical techniques, long-term survival has barely improved. Median survival after surgery alone is about 6 months, with only 7.5% of patients living 2 years. Adding radiation extends median survival to roughly 9 months, while systemic chemotherapy has shown minimal benefit [61,62]. Chemotherapy is a key part of cancer management, but treating brain tumors is especially hard because of the blood-brain barrier. Most anticancer drugs are large, charged, or hydrophilic, so they cannot cross the BBB. To reach therapeutic levels in the CNS, you would need systemically toxic doses. Local delivery directly to the tumor site avoids this problem, which is particularly useful for solid tumors.

BCNU, a nitrosourea, is considered the "gold standard" for local brain tumor treatment even though it has a very short half-life. To deliver it effectively, it is incorporated into a polyanhydride matrix of poly[bis(p-carboxyphenoxy) propane-co-sebacic acid], or P(CPP:SA), at a 20:80 molar ratio. This product is Gliadel: a sterile, off-white to pale yellow wafer, 1.45 cm in diameter and 1 mm thick.

When BCNU is given systemically, its half-life is only about 12 minutes, making conventional delivery impractical. But when released from the Gliadel polymer wafer, BCNU concentrations in the brain are orders of

magnitude higher than what systemic dosing could achieve. The drug is delivered locally over 2–3 weeks with minimal systemic toxicity.

6.1.2 CLINICAL LIMITATIONS

- **Rapid Clearance:** The drug suffers from the "sink effect," meaning once it is released, it can be quickly washed away by the systemic circulation or diluted by cerebrospinal fluid.
- **Complications:** The localized implantation can sometimes induce severe, symptomatic local brain edema (swelling) and other neurological deficits.
- **Sink Effect:** Over time, the drug can get washed away by systemic circulation, potentially subduing the long-term impact on aggressive cancers.
- **Shallow Penetration:** The drug relies on passive diffusion, which only penetrates a few millimeters into the surrounding brain tissue, leaving deeper, highly invasive cells untouched.
- **Edema & Complications:** Placement can sometimes cause localized cerebral edema (brain swelling) or obstruct cerebrospinal fluid (CSF) flow.

6.1.3 INDICATIONS

Gliadel is currently FDA-approved for two main applications:

- Newly Diagnosed High-Grade Glioma: Used as an adjunct to surgery and standard radiation therapy.
- Recurrent Glioblastoma: Used as an adjunct to repeat surgery to slow localized progression.

6.1.4COMPARISON TABLE OF SYSTEMIC VS GLIADEL BCNU PHARMACOKINETICS

Parameter	Systemic BCNU (IV)	Today CNU (Local Wafer)
Route of administration	Intravenous infusion	Implanted directly into tumor resection cavity
Half-life	~12 minutes in plasma	Release sustained over 2–3 weeks from P(CPP:SA) matrix
BBB penetration	Poor. BCNU is lipophilic but rapidly cleared. Requires very high systemic dose to get measurable CNS levels	Bypasses BBB entirely. Drug released directly at tumor site
Peak brain concentration	Low: ~0.5–1 µg/g tissue. Drops fast due to short t½ and systemic clearance	Very high: 100–1000x higher than IV. ~15–20 µg/g tissue reported near implant
Duration above therapeutic level	Minutes to <1 hour	14–21 days of continuous release as polymer surface erodes

Systemic exposure /toxicity	High. Dose-limiting myelosuppression, pulmonary toxicity, nausea. Max tolerated dose ~200 mg/m²	Minimal. Systemic BCNU levels <5% of IV levels. Major toxicities avoided
Drug distribution	Whole body. <5% of dose reaches brain	Localized to ~1–2 cm radius around wafer. Creates high local gradient
Mechanism of clearance	Hepatic metabolism + renal excretion. Very rapid	Polymer erosion + local tissue metabolism. Follows zero-order from P(CPP:SA) surface erosion
Clinical impact	Median survival with radiation + IV BCNU: ~9–12 months. Minimal added benefit over radiation alone	Median survival with radiation + Gliadel: ~13–14 months. 2-year survival ~16% vs 8% for placebo wafer

6.1.5 APPLICATIONS

- **Primary Treatment for Glioblastoma (GBM):** Implanted directly into the surgical cavity following the resection of malignant brain tumors. Up to 8 wafers are placed along the walls and floor of the cavity.
- **Management of Recurrent Gliomas:** Utilized as a salvage or adjunctive therapy for tumors that have returned after initial treatments.
- **Adjuvant Multimodal Therapy:** Used alongside systemic therapies (e.g., Temozolomide) and standard radiation therapy to prevent tumor recurrence.

6.2 SEPTACIN

Septacin is a specialized, biodegradable sustained-release implant used in orthopedic procedures to treat bone and soft tissue infections, such as osteomyelitis.

It uses a specific polyanhydride matrix to release antibiotics directly at the disease site over an extended period.

6.2.1MECHANISM OF ACTION

- **Controlled Hydrolysis:** The polyanhydride degrades via surface erosion when exposed to bodily fluids. As the polymer slowly breaks down through hydrolysis, it releases the trapped antibiotic in a sustained, controlled manner.
- **Site-Specific Efficacy:** By delivering medication directly to the site, it achieves extremely high local drug concentrations that are impossible to reach via oral or intravenous administration.

- **Reduced Systemic Toxicity:** Delivering the drug locally avoids widespread systemic exposure, greatly reducing the severe kidney or liver toxicities often associated with prolonged, high-dose antibiotic therapy.

6.2.2 ROLE OF SEPTACIN IN LOCALIZED DRUG CARRIER SYSTEM

- **Targeted Antibiotic Delivery**: By implanting Septacin directly into the infected bone cavity after surgical debridement, antibiotics are released locally. This avoids the systemic side effects often seen with oral or intravenous administration.
- **Controlled and Sustained Release**: The polymer matrix (typically made of polyanhydride chemistry) breaks down slowly over time. This ensures a continuous, steady release of the active medication at the infection site for days or weeks.
- **Biocompatible Degradation**: Septacin degrades into biocompatible, non-cytotoxic, and non-mutagenic acidic byproducts. Because the carrier simply dissolves into harmless metabolic substances, a secondary surgery to remove the implant is unnecessary.
- **Reduces Antibiotic Resistance**: By maintaining a highly concentrated local dose of the antibiotic, it acts more effectively against resistant bacterial biofilms compared to relying solely on drugs circulating through the bloodstream.

Septacin is a PA implant consisting of P(FAD:SA) (1-to-1 weight ratio) polymer and gentamicin, as active agent, for local delivery to infected bone (osteomyelitis). It is designed for local delivery to infected bone in cases of osteomyelitis. The implant is supplied as strands, with each strand containing five beads connected by linkers. Each bead is 12 mm long, 4 mm in diameter, and weighs about 150 mg, containing 20 mg of gentamicin as gentamicin sulfate. The matrix is prepared using a melt mixing procedure, and injection molding machines are used for further processing. Large-scale production is carried out on automated equipment that includes a twin-screw extruder, gravimetric feeders, cooling conveyors, a pelletizer, and production-scale injection molding machines. The final product is packed in plastic blisters and sealed in aluminum stir pans. Sterilization is performed using gamma radiation. Stephens et al. conducted a detailed study of drug release from Septacin implants, which revealed the complex nature of EAD/SA dissolution and gentamicin release from the PA matrix. Drug release was faster in water than in pH 7.4 phosphate buffer. For in vivo evaluation, a pharmacokinetic study was done by implanting either one or three Septacin beads in the backs of Sprague-Dawley rats. Release was tracked for 6 weeks post-implantation, and gentamicin release was essentially complete by the fourth week. Plasma levels of gentamicin remained minimal throughout. After 2 weeks, there was no difference in the plasma profiles between one bead and three beads, which highlights the benefit of localized drug delivery [63]. Interestingly, the in vivo release profile matched the in vitro profile in water more closely than the profile in pH 7.4 buffer. The product is packed in plastic blister and finally sealed in aluminum stir pans. Sterilization is done by γ -radiation [64]. Stephens et al

6.2.3 LIMITATIONS OF SEPTACIN IN LOCALIZED DRUG CARRIER

its primary limitations include the risk of generating antibiotic-resistant bacteria, invasive surgical removal in some cases, and hydrolysis-driven chemical instability. However, the key limitations are

- **Sub-therapeutic Dosing & Resistance:** Localized antibiotic delivery can cause an initial burst release followed by prolonged sub-inhibitory drug levels that promote resistance.
- **Hydrolytic Degradation & Stability:** Septacin relies on a polyanhydride matrix (typically poly (sebacic acid) or related copolymers). Anhydride bonds are highly reactive to water and undergo

hydrolytic cleavage, which means these carriers generally suffer from a limited shelf-life and strict storage requirements (e.g., maintaining at cool temperatures under inert gas to prevent degradation).

- **Potential for "Burst" Release:** Polyanhydride matrices frequently exhibit a rapid "burst" of the drug immediately after implantation, before settling into a slower, sustained release. This initial dump can cause localized tissue toxicity or deplete the drug reservoir too quickly.
- **Invasive Retrieval:** Depending on the specific formulation, carrier fragments or degraded remnants may physically block tissue healing or necessitate a secondary, invasive surgical procedure to extract the spent delivery device.
- **Narrow Clinical Application:** The use of such localized drug-delivery implants is typically limited to well-defined, surgically accessible cavities (e.g., debrided bone defects). They cannot treat diffuse or widely spread infections.

. carried out a detailed study for drug release from Septacin implants and revealed the complex nature of EAD/SA dissolution and gentamicin release from a PA matrix [65]. Drug release was faster in water than in pH 7.4 phosphate buffer. This is contrary to what would be predicted based upon the relative copolymer hydrolysis rates and monomer solubilities in these two different dissolution media. Fitting the in vitro drug release data to the Peppas model indicated anomalous release in water and diffusion-controlled release in pH 7.4 phosphate buffer. In addition, the beads cracked in water, while cracking was not observed in pH 7.4 buffer. Drug

release was not governed by surface erosion only and the study corroborates the results reported by Park et al [66,67].

6.2.4. CLINICAL INDICATIONS

- **Chronic and Acute Osteomyelitis:** It delivers a highly concentrated, localized dose of antibiotics directly to the infected bone and marrow. This bypasses the need for long-term, high-dose systemic (oral or intravenous) antibiotic therapies.
- **Bone and Soft Tissue Infections:** It serves as a potent adjunct (and sometimes alternative) therapy where systemic antibiotics struggle to penetrate dense or necrotic bone tissue.

6.2.5 ADVANTAGES OF THE SEPTACIN SYSTEM

- **Bypasses Toxicity:** By confining the antibiotic to the surgical site, it minimizes the systemic side effects and organ toxicity often seen with prolonged IV antibiotic use.
- **Bacterial Penetration**: It overcomes the poor vascularization characteristic of infected bones, ensuring a high, sustained therapeutic concentration precisely where it is needed.
- **Surface-Erosion Kinetics:** Septacin undergoes a predictable surface-erosion process, releasing the antibiotic at a constant rate rather than a sudden "burst" that might be toxic or ineffective.
- **High Local Concentration**: By placing the drug-loaded polymer directly into the surgical site (e.g., bone cavities), it delivers highly concentrated antibiotic levels exactly where they are needed while sparing the rest of the body.
- **No Toxicity from Degradation**: The polyanhydride breaks down into naturally occurring fatty acid byproducts that are non-toxic and easily eliminated by the body.
- **Reduces Systemic Burden**: Avoids the need for long-term intravenous antibiotics, thereby reducing side effects on the kidneys and liver.

7. POLYANHYDRIDES UNDER DEVELOPMENT

Since the pioneering work by Langer in the 1980s, PAs have been investigated extensively for application in various biomedical fields [68]. Complications of all the research work on various types of PAs have been made in the form of reports and reviews. We have divided these recent PAs on the basis of monomeric unit or block unit attached to the main PA chain:

- Amino acid based;
- Photo-polymerizable PAs;
- Ricinoleic acid;
- Salicylate based; and
- Succinic acid based.

7.1 AMINO-ACID BASED PA'S

Amino acid–based polyanhydrides were first reported in the 1990s by Domb [69]. Recent progress in this class has focused on developing crosslinked PAs that are suitable for in vivo use. Earlier versions used alanine-containing crosslinked PAs, where crosslinks were formed by irradiating methacrylated end groups. The problem was that hydrolysis of those networks produced non-biodegradable fragments with limited biocompatibility, which restricted their use in the body. To overcome that, new crosslinked amino acid PAs were designed to contain only anhydride bonds. Anhydride linkages are hydro labile, so the entire crosslinked network can break down into water-soluble, biocompatible degradation products.

One example is a crosslinked PA based on N-trimellitylimido-glycine (TMA-gly) and sebacic acid (SA). These were synthesized by copolycondensation using a 1,3,5-benzenetricarboxylic acid (BTC) prepolymer as the crosslinking agent. Crosslinking was confirmed by differential scanning calorimetry, which showed a single melting peak for the polymer. To prevent phase separation and ensure a homogeneous polymer matrix, a monomeric SA prepolymer was prepared before copolymerization.

7.2 PHOTO POLYMERIZABLE PA'S

Photo-crosslinking is preferred over chemical crosslinking specifically in in-situ polymerization processes to avoid the adverse effects of chemicals generated during chemical polymerization. The other advantage of photo-initiated polymerization over than the other crosslinking techniques is spatial and temporal control of the polymerization, which allows the precise control of polymer formation by directing and shuttering the light source. These reactions are rapid enough to overcome oxygen inhibition and moisture effects and can be controlled over a time frame of seconds to minutes. Anhydride monomers with reactive metacrylate functionalities Have been developed and used for the preparation of PAs which shows in-situ crosslinking on exposure to light. These systems were demonstrated to be biocompatible and were used for bone augmentation applications [70,71].

Shastri et al have prepared a new family of photo-chemically cured PAs which can produce semi-interpenetrating degradable networks, and evaluated them for biocompatibility in subcutaneous tissue in rats. This system appears to undergo degradation primarily by surface erosion. Photo-crosslinking gives "cure-on-command" PAs. Inject a liquid prepolymer, shine light, and it solidifies exactly where and when it is required — with no toxic initiators left behind. And because the backbone is still all anhydride bonds, which keep the surface erosion profile that made PAs famous in Gliadel.

7.3 RICINOLEIC ACID (RA) BASED PA'S

Incorporating fatty acids into a biodegradable polymer backbone is advantageous, but it's limited because most naturally occurring fatty acids are monofunctional. Unsaturated monofunctional fatty acids first have to be converted into dimers before they can be polymerized. Ricinoleic acid (RA) was found to be a more suitable alternative for synthesizing fatty acid–based polyanhydrides. RA is one of the few commercially available fatty acids that contains an additional 12-hydroxy group. That makes it bifunctional — it has both a hydroxyl group and a carboxylic acid group — so it can be incorporated directly into the PA backbone through ester bond formation, without needing prior dimerization RA-based polymers, first studied in the late 1990s, are the newest members of the polyanhydride family. However, the early RA polymers were made as solid implants, which require surgical intervention to place in the body. Incorporation of fatty acid in the biodegradable polymer backbone is advantageous but it is restricted by monofunctionality of most naturally occurring fatty acids. The unsaturated monofunctional fatty acids first need to be converted to dimer for further polymerization. The dimer contains a branched C-C linkage which cannot be metabolized by the body and the dimer may remain in the body for 6 months [72]. RA (cis -12-hydroxyoctadeca-9-eonoic acid) was found to be the most appropriate alternative for the synthesis of the fatty acid-based PAs.

Recent work has shifted toward converting this solid form into a liquid injectable form. The goal is a formulation that can be injected and then form a solid or semisolid implant in situ after Administration [73]. Most fatty acid PAs need a dimerization step that adds cost and complexity. RA skips that step and brings built-in hydrophobicity + flexibility from the long C18 chain. The 12-OH, also lets you tune degradation by controlling ester vs anhydride bond ratios in the backbone.

7.4 SALICYLATE-BASED PA'S

These salicylate-based polyanhydrides are collectively referred to as "PolyAspirin" because they hydrolytically degrade into salicylic acid, a non-steroidal anti-inflammatory drug (NSAID). Salicylic acid–based polymers are a unique example of polymer therapeutics where the drug itself is integrated into the polymer backbone. Amino salicylic acid is a useful bioactive agent for inflammatory bowel disease, and it needs to be delivered specifically to the site of action — the colon. Synthesis of this class of polymers is generally done by first preparing prepolymers, followed by melt condensation to produce high molecular weight polymers.

However, Schmeltzer et al. modified the synthesis method. They altered both the reaction conditions and the condensation step to include dynamic mixing of the reactants, which gave higher molecular weight polymers [74]. The reaction was later modified again to a milder form. In that version, PA prodrugs with glass transition temperatures of 35.7–44.0°C were prepared by reacting salicylic acid or diflunisal with C10–C18 diacid chlorides in the presence of a base. Polymerization of the diacid intermediate was then carried out with a base and a coupling agent. This class of polymers has also been synthesized using various salicylic acid derivatives, including halogenated salicylates, amino salicylates, salicylsalicylic acid, and thiolsalicylic acid. The poly(anhydride-esters) was made by melt condensation polymerization. Among these, the halogenated salicylate derivatives gave the highest molecular weight polymers and the highest glass transition temperatures. All of these derivative polymers showed in vitro degradation lag times of 1 to 3 days, depending on the water solubility of the specific salicylate derivative used. Most drug delivery systems have drug + polymer. Here, the polymer _is_ the drug. When the anhydride/ester backbone erodes, you don't get inert monomers — you get salicylic acid right at the disease site. For IBD, that means colon-targeted anti-inflammatory action with minimal systemic exposure.

7.5 SUCCINIC ACID BASED PA'S

Recently, succinic acid based functional polymers was have been synthesized with allyl pendent group, which can be utilized for further co polymerization or attachment of other moieties to perform specialized function. Succinic acid is a naturally occurring substance in living tissues, so polymers made using it can be inherently biodegradable and biocompatible. Succinic acid has been incorporated into polymer chains for several different functions. Initially, it was used to convert monocarboxylic monomers into dicarboxylic ones to enable polymerization [75,76]. For example, ricinoleic acid was modified this way to help the polymerization reaction. In another approach, succinic acid's chloride derivative was reacted with p-hydroxycinnamic acid to make a fluorescent monomer. That monomer was then copolymerized with sebacic acid to give a fluorescent polymer. Particles made from this polymer can help researchers track and understand their behavior in various biomedical applications. Increasing the ratio of the fluorescent monomer also slowed the degradation rate, which can be used to tune drug release behavior [77]. In, earlier work, succinic acid was used directly as one of the monomer units. For instance, Ben-Sabat et al. synthesized copolyanhydrides from trimers of fumaric acid, succinic acid, and propylene glycol. These polymers degraded and released the entrapped drug within about a week. In vivo testing in rats showed the polymer was safe, supporting further investigation as a drug delivery carrier. Succinic acid derivatives have been used more widely to synthesize unsaturated and functional polymers. Copolymers of 2-hexadecylsuccinic acid and sebacic acid were prepared using the standard melt condensation method and were shown to be potential carriers for localized drug delivery. More recently, succinic acid–based functional polymers have been synthesized with allyl pendent groups. These groups can be used for further copolymerization or for attaching other moieties to give the polymer specialized functions [78].

Succinic acid is a "molecular adapter." It turns mono-acids into di-acids for polymerization, adds fluorescence for tracking, introduces double bonds for crosslinking, and keeps everything biocompatible because it's already in the Krebs cycle.

CONCLUSION

From recent updates on polyanhydrides, it can be concluded that these polymers have great potential as localized drug delivery carriers due to the versatility of their properties. However, the challenge of stabilizing the system to achieve a long shelf life is still ongoing. In this article, various polyanhydrides have been discussed, with major emphasis on their use as localized drug delivery systems. Because anhydride bonds are labile, these polymers are highly susceptible to hydrolysis. This property has made them useful as surface-erodible carriers for drug delivery. Their surface erosion behavior also gives them the advantage of near zero-order release, which is a benefit over many other systems.

Despite these advantages, very few polyanhydrides have reached the market. The main commercial examples are Gliadel wafers and Septacin beads. In both products, drug release is controlled by tuning the hydrophobic-hydrophilic balance to regulate hydrolytic degradation. A few new PA-based systems are emerging. Injectable ricinoleic acid–based polyanhydrides are in advanced stages of development and may reach the market soon. These could become important carriers for anticancer agents and other drugs, functioning as depots for controlled drug delivery over extended periods.

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