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Polyanhydrides as localized drug delivery carrier: an update

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Background: There is a continuing thrust to increase the efficacy and reduce the toxicity of existing and new drug molecules for their better usage to treat disease. Localized drug delivery has been explored in the same way, which can provide a platform to target local diseased tissues and can reduce the burden on the body by reducing the dose size and hence the dose-related toxicity of the molecules. Various polymers have evolved for the purpose of localized drug delivery, however, polyanhydrides are considered the best, supported by products in the clinical phases. *Objective*: To demonstrate the advantages of localized delivery using basic concepts and describing polyanhydride carrier with products such as Gliadel® and Septacin™. *Methods*: The rationale behind localized drug delivery and the carrier for the same are dealt with. Polyanhydrides discussed in detail are those from subclasses that have been given less emphasis previously and have been developed or investigated in the last 5 years. *Results/conclusion*: From the recent update 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 quest to stabilize the system in order to achieve a long shelf life remains ongoing.

Keywords: drug delivery, Gliadel®, implants, localized carriers, polyanhydrides, Septacin™ surface eroding polymers

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1. Introduction

The use of polymers in the field of biomedicine has grown massively, with major applications such as surgical devices, implants and supporting materials (e.g., artificial organs, prostheses and sutures), drug delivery systems with different routes of administration and design, carriers for immobilized enzymes and cells, biosensors, components of diagnostic assays, bioadhesives, ocular devices and materials for orthopedic applications [1-6]. Drug delivery is one of the most benefited areas, which has grown along with the advancement in polymer science. The use of polymers in drug delivery has not been restricted to additives, but they have gained enormous importance as an entire matrix for delivering drugs/biomolecules. The increasing interest in using polymers is due to the flexibility they offer to achieve the properties suitable for varied clinical needs. One such clinical need is the treatment of ailments that are localized to a particular site in the body, for example cancer (especially solid tumors) [7,8], thrombosis, restenosis [9], osteomylitis [10], local infections [11,12], glaucoma and retinal disorders [13]. Conventionally, drugs in these disease conditions have been given in a manner in which they reach the local site only via systemic circulation, but more often than not the drug is required at the affected site only. This kind of treatment is not an efficacious use of the drug, and more importantly gives rise to adverse effects, which can sometimes impel discontinuation of the therapy. To overcome this off-target and inefficient use of drugs, the concept of a 'magic bullet' came into existence and a huge

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amount of knowledge has been shared in the literature in the form of research work and discussions about this particular concept. The approach of targeting near to the drug or, in other words, presenting the drug near/into the disease site, is a step towards this 'holy grail'. Drugs administered locally give a maximum concentration at the site of action where it is actually required and at the same time a minimum amount of the drug reaches the systemic circulation to cause adverse effects. This can be accomplished using a polymeric drug delivery system. Both biodegradable and non-biodegradable (in terms of residence time in the body) polymers have been explored, however the biodegradable class of polymers is preferred because of the obviation of device removal from the body after a certain time period, which may otherwise lead to polymer load on the body.

Various biocompatible biodegradable polymers like polyesters, polyanhydrides (PAs), polyortho-esters, polyphosphezenes, etc. have been studied over the last few decades and recently some of them have reached clinic or various clinical phases. These polymeric materials have been used both for systemic and localized controlled drug delivery, but in the latter case erosion of polymeric device (loss of matrix) with drug release would always be an implied property. In such a condition, PAs meet the requirements due to their surface eroding property that in turn is due to the high water lability of the anhydride bond. Various types of homo- and hetero-PAs consisting of aliphatic, aromatic, heterocyclic and other monomers have been studied in detail and extensive work on PA carriers resulted in clinically used implants like Gliadel® (MGI Pharma Inc., Bloomington, MN) and Septacin™ (Abbott Laboratories, North Chicago, IL). This success spurred further research in the area, with some recent additions including liquid polymers utilizing naturally available fatty acids which function on the basis of sol-gel mechanism and PAs having polyester and polyether in the backbone. These new polymers have an important role in drug delivery because of their favorable drug release (it can be tailored), degradation and toxicity profiles. All these recent developments in PAs have opened new vistas to the use of this polymer class in drug delivery applications. Gliadel and Septacin are two emblematic examples of the use of PA in localized drug delivery; the former is used in gliomas (brain cancer) while the latter is useful for treating osteomyelitis infection. Gliadel contain P(CPP:SA) (20:80) whereas Septacin has P(EAD:SA) (50:50) as a polymeric carrier and the active molecules are BCNU and gentamicin sulfate, respectively. The success of Gliadel in the market without any reports of Phase IV (post-marketing surveillance) complications has lead to further interest in this polymer class, and the recent polymers with their formulated drug delivery systems may also reach the market soon.

In this article, the need for and advantages of localized drug delivery are addressed. In addition polymers, especially PAs, which are useful in such delivery, are examined. PAs are discussed in detail with various subclasses, recent advancements and clinically used products.

2. Localized drug delivery: biopharmaceutical and pharmacokinetic advantages

Although drug discovery research has advanced from the conventional lengthy approach to high-throughput screening (HTS) and ultra high-throughput screening (UHTS) to find new targets and drugs, nevertheless developing a new drug is still a tedious, time-consuming and much costlier job than exploring a viable drug delivery system. Thus, there has been a paradigm shift in the drug discovery and development program towards more efficient delivery of old drugs for maximum therapeutic benefit and minimum adverse effects, and giving these molecules a 'new life'. The effectiveness of a drug, when given systemically, is dependent upon its concentration within a specific therapeutic range, above which toxicity or other side effects dominate and below which the concentration is too small to provide the significant benefit of the drug molecule. However, maintaining drug concentrations is complicated by metabolism or consumption of the drug. Therapeutic levels are often maintained by multiple administrations. The faster a drug is metabolized or consumed, the more difficult it is to maintain therapeutic concentrations by multiple administrations. All of these issues can be resolved, for localized diseases, by a single dose at the target site.

Localized drug delivery offers many advantages (**Figure 1**), with the main improvement being in high locoregional concentration of therapeutic agent/s with prolonged retention (especially for drugs with high extraction ratio) [14]. 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 [15]. The latter approach is preferred as it requires minimum effort in terms of selecting excipients/active ingredients and easy formulation. 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 high systemic dose to achieve the same drug concentration at the diseased tissue site [14,16]. 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 [17]. 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. For drugs with dose-dependent activity, localized delivery can help in reducing side effects at non-target sites without compromising the therapeutic benefit at the site of action. Further, there are some disease conditions where localized delivery is a physiological requirement. For example, in bone injury cases, insufficiency in local blood supply due to post-traumatic or post-operative tissue damage and inadequate tissue penetration leads to ineffectiveness of systemic antibiotic therapy, both in terms of preventive or curative drug administration.

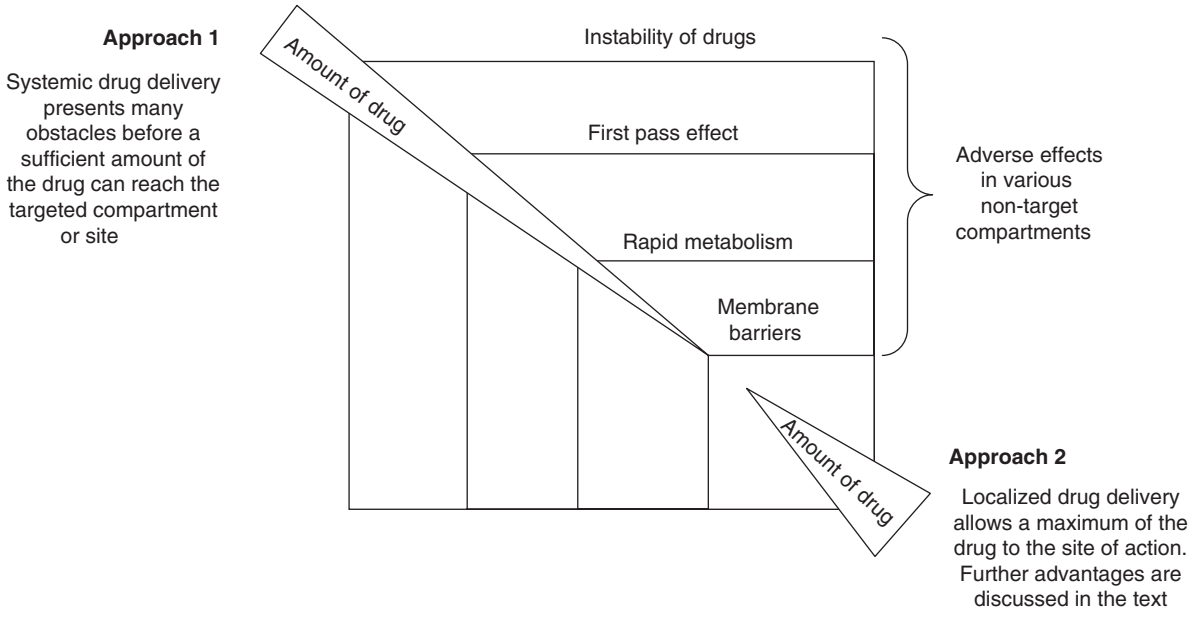


Figure 1. Schematic diagram representing advantage of localized drug delivery over systemic delivery. More efficiently use of drug in former case in terms of barriers to overcome and minimal/no adverse effects.

One important example is anticancer drugs, where tumoral delivery is limited by poor blood supply caused by radiation therapy or surgery. Anticancer drugs pose another challenge of pre- and simultaneous medication because of their deleterious effect on other organs. Because of the many complications involved in the systemic chemotherapy of malignant tumors, localized delivery remains the simplest solution [18]. Finally, if the carrier is a biocompatible, resorbable polymer, then this obviates the need for removal of the implant or the system after the release of the drug. Polyanhydrides give the additional advantage of limited exposure before releasing the active agent due to its surface or heterogeneous degradability. Recent PAs possessing sol-gel properties have a further advantage of injectability and thus surgical intervention is not required to introduce the delivery system to the affected site.

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:

- being hydrophobic enough so that it can hold the drug molecule and release the drug in a predictable and controlled way;
- being biocompatible when implanted in the target organ;
- being eliminated completely from the implantation site in predictable time;
- having suitable physical properties for the device fabrication (low melting point, usually below 100°C, and soluble in common organic solvents);
- being flexible enough before and during degradation so that it does not crumble or fragment during use; and
- being easy to manufacture at a reasonable cost [19-21].

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 [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. Considering the degradation/erosion property, polymers can be mainly divided as homogeneous/bulk degrading polymers and heterogeneous/surface degrading polymers. A particular type of behavior can be explained on the basis of the chemical structure of the polymer backbone and the functional groups present. Polyesters like PLA, PLGA, PCL, etc., degrade by

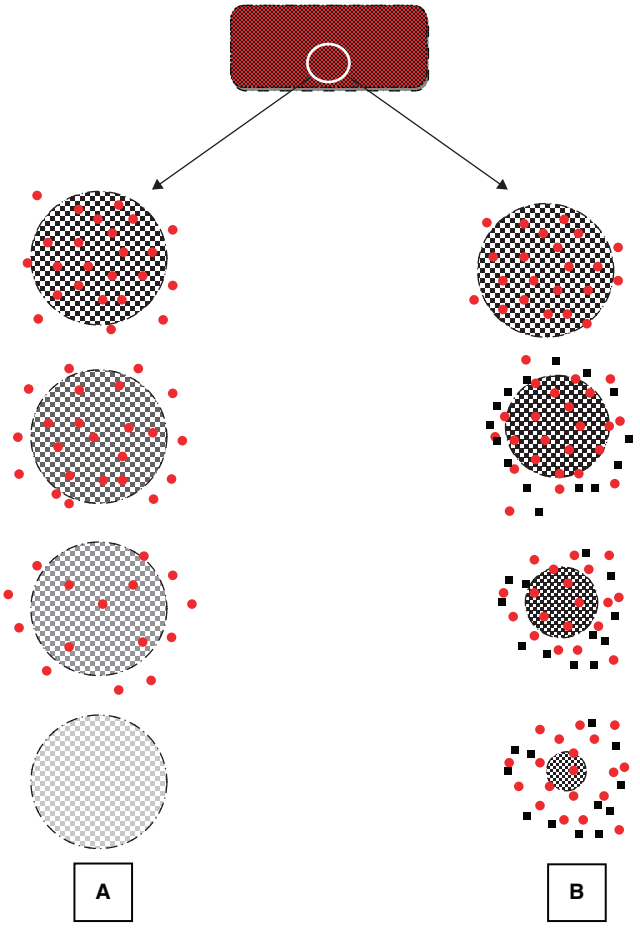


Figure 2. Depiction of drug release and polymer degradation from a polymeric drug delivery system. Black squares and red circles represent the polymer matrix and drug, respectively. (**A**) is homogeneous/bulk erosion where drug release occurs without polymer mass loss, which occurs slowly and continues 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.

homogenous pattern or bulk erosion wherein the drug release occurs without significant loss of polymer mass and polymer volume, whereas PAs degrade by a surface erosion mechanism in which both polymer degradation and erosion occur simultaneously, which leads to the greater release of the drug from the surface (**Figure 2**). PLGA is the most studied biodegradable polymer and various delivery carriers such as microspheres, nanoparticles, nanofibers, etc., have been developed for controlled release applications. Thus, surface eroding polymers may be the better option for developing such kind of system because of their greater ability to achieve close to zero-order release kinetics and to protect hydrolytically sensitive molecules by encapsulation. In localized drug delivery, it will be an added advantage if the polymer not only degrades but also erodes form the implantation site to cause minimum damage to the tissue and to prevent over-exposure of the biomaterial to a particular type of cells. PAs are expected to release the drug at a constant release rate which is directly proportional to the polymer erosion rate. For a surface-eroding device, the polymer must be hydrophobic and have water labile linkages which can undergo hydrolytic degradation. 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]. Polyanhydrides are believed to predominantly undergo surface erosion due to: i) the high water labiality of the anhydride bonds on the surface; and ii) hydrophobicity, which restricts water penetration into the bulk. High hydrolytic reactivity of the anhydride linkage provides an intrinsic advantage in versatility and control of degradation rates over other classes of bioerodible polymers. 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 fold by simple changes in the polymer backbone and by altering the hydrophobic and hydrophilic balance of the polymer [28,29]. Aliphatic PAs degrade in a few days while some aromatic PAs degrade over few years. Degradation rates of copolymers of aliphatic and aromatic PAs vary between these extremes and this feature of PAs gives an opportunity for making a drug delivery system that can provide the release of drugs for a desired time length of treatment.

3.1 Degradation of polyanhydride

Polymer degradation is always a vital parameter to its selection for a particular application as it decides the fate of the drug delivery system in terms of life of the system, disposition in the body, storage conditions, drug release kinetics, etc. Chemically PAs are made up of hydrophobic monomers connected via very hydro-labile anhydride bonds which are responsible for faster degradation of the polymer at the surface of the device and which make it a most suitable polymer class for localized drug delivery. The basic pH of the surrounding medium enhance degradation tremendously by a two-tier effect: first the reaction is base catalyzed; and second the higher solubility of acid degradation products moves these products away from the degrading matrix [25]. Although PAs degrade by surface erosion, there are many factors that influence the mechanism and rate of degradation, for example the type of monomers and their composition. Generally in polymers, amorphous polymer areas erode faster than crystalline ones and PAs are no exception to this [30]. All aliphatic PAs are rigid, crystalline material and their melting point increases with their monomer chain length, however faster degradation rates poses a limitation in their pharmaceutical applications, except in some aliphatic PAs such as P(FA:SA) which has bioadhesive properties. In contrast, aromatic PAs are high melting polymers and degrade very slowly, thus the combined properties of aliphatic

and aromatic PA have been used to obtain a copolymer with improved mechanical characteristics and adjustable erosion times [28,31]. The most prominent example is a copolymer of P(CPP:SA), used in Gliadel, which has been reported to release the drug via a surface erosion mechanism [26,32]. The erosion velocity of P(CPP:SA) decreases with increasing CPP content. Erosion zones in P(CPP:SA) are highly porous and separated from non-eroded polymer by erosion fronts which move at a constant velocity from the surface of a matrix into its center [25]. Fatty acid based polymers forms an important class of PAs and P(FAD:SA) is one of the most studied copolymer out of this class; these have also shown erosion zone, but due to the low solubility of FAD, the erosion zone mainly consisted of a semisolid mixture of FAD and FAD salts, instead of a porous erosion zone. The semisolid layer forms a permeation barrier and sebacic acid was found to precipitate inside the erosion zone; this ultimately leads to the slow release of SA as well as the drug. Ricinoleic acid based PAs have been reported to undergo a sharp decrease in molecular weight during the first 24 h of erosion *in vitro* and lost 40% of their anhydride bonds in 48 h [27,33]. Whereas the degradation process of poly(ester-anhydride)s made from RA and SA progresses in two stages. In the first stage, which lasts for about one week, the anhydride bonds are fully degraded, releasing the SA units conjugated in both of their carboxylic acids by anhydride bonds. In the next step, the remaining RA–RA or RA–SA oligoesters degrade into shorter RA ester dimers, trimers and tetramers as well as dimers of RA–SA, which are dissolved in the degradation aqueous medium [34]. Polyanhydride chain terminated with linear fatty acid like lauric, oleic or stearic acid also show an exponential loss of molecular weight and erosion behavior similar to ricinoleic acid based polymers [35,36]. The increase in amount of fatty acid and the chain length induced the bulk erosion properties of PAs [25]. The photo-crosslinked PA obtained from metacrylated SA, metacrylated CPP and metacrylated CPH showed a linear erosion profile when eroded *in vitro* [37,38] and degradation behavior was slowed down by blending hydrophobic linear polymer polymers (e.g., poly(methyl metacrylate)) and excipients like cholesterol and steric acid. Crosslinking in amino acid based PAs was found to have minimum effect compared to their linear counterparts, whereas inclusion of amide bond into the backbone was found to reduce the degradation rate significantly [39,40]. Salicylate-based polymers show a lag time of 1 – 3 days before degradation sets in, followed by surface degradation. Faster degradation of PAs is a useful characteristic in salicylate-based polymers as it allows targeting in the colon, where pH is high, for inflammatory bowel disease [41,42]. Succinic acid based PAs usually degrade in a week, however the presence of pendent group affects this property according to their nature [43,44]. The geometry of the PA device also affects the PA degradation and the relationship of a lower rate of degradation for bigger matrices than smaller matrices due to surface area difference is well reported [45,46]. For example, during *in vitro* erosion of microspheres made of p(FAD-SA) 8:92, p(FAD-SA) 25:75 and p(FAD-SA) 44:56 with average diameters below 100 μm, SA was released completely in 100 h, while the release time was in weeks from a matrix form of the polymer [47]. Theoretical and computational models including the Monte Carlo based calculation have also been proposed to predict degradation and erosion of PA device [48-52].

4. Types of polyanhydrides

Polyanhydrides were discovered as early as 1909 by Bucher and Slade [53] in the form of aromatic PAs, however these were first explored by Conix after almost 50 years to form fibers for textile application [54]. Although Hill and Carothers [55] had worked in the 1930s on aliphatic PAs of adipic and sebacic acid, because of hydrolytic instability, no further development was carried on these polymers until they were explored by Langer in the 1980s for drug delivery [56,57]. Heterocyclic PAs were also developed in the meantime by Yoda *et al.* with good film and fiber-forming properties [58]. Once the degradable and biocompatible nature of PAs was uncovered, various types of copolymers were prepared thereon and utilized in drug delivery by Langer, Brem, Domb and co-workers. One of the simplest classifications for PAs can be homo- and hetero-PAs, however in the development of erodible materials, the use of copolymers (hetero-polymers) is important for their different erosion rates, enabling the achievement of different target times for release, and this is possible by using different monomers and their ratio. In most PA copolymers, aliphatic chain used is composed of polysebacic acid (PSA) and thus these are classified on the basis of the other part of the copolymer, which in turn governs the polymer properties. Increasing hydrophobicity of the monomer makes the polymer more stable in terms of hydrolytic degradation because of less penetration of water molecules. Aromatic PA P(CPP-SA) is one of the most studied and explored polymers, which also resulted in Gliadel [28,31,59,60]. Other aromatic PAs studied in this series are P(CPH:SA), P(CPM:SA), P(CPV:SA). Among other aliphatic–aromatic PA copolymers are those based on the common diacids isophthalic acid (IPA), terephthalic acid (TA) and fumaric acid (FA) [23]. These copolymers are highly soluble in chloroform or dichloromethane, melt at temperatures above 250°C, and are stable upon storage at 25°C and exposure to 2.5 Mrad of γ–radiation. Copolymers of fumaric acid with aliphatic diacids such as sebacic acid are less crystalline and soluble in chlorinated hydrocarbons [61].

Another important group of PAs used for controlled drug release applications is fatty acid based PAs. This class of PAs has also been developed and studied extensively, resulting in many subclasses. The first subclass is linear and nonlinear fatty acid terminated PAs [35,36]; the second is fatty acid dimer based, in which the majority of the studies are focused on erucic acid based copolymers [21,62,63]. Oleic acid and

linoleic acid are other fatty acid dimers used with sebacic acid as a drug delivery system [64]. The third subclass, a recent addition, is ricinoleic acid based PAs, most of which possess the desired physicochemical properties such as low melting point, hydrophobicity and flexibility of the polymer for their localized injectable use [27,33,65-67]. Many polyester–anhydrides have been prepared from ricinoleic acid derivative and found suitable for direct injection to the site of action [68]. This subclass is discussed in more detail below.

Another recent addition, or the PAs that have been explored as a new class in the last few years, involve the inclusion of amino acids such as glycine and alanine into the polymer backbone to increase the mechanical properties. The amino acids are incorporated by imide bonds at the amino terminus, leaving the terminal carboxylic acids available for activation. This poly(anhydride-imides) appear to undergo predominantly surface erosion [39,40,69,70]. Crosslinked amino acid containing PAs based on TMA-ala (*N*-trimellitylimido-b-alanine) or TMA-gly and sebacic acid were synthesized by copolycondensation using BTC (1,3,5-benztricarboxylic acid) prepolymer as a crosslinking agent. Succinic acid based PAs adds to this class of polymers by allowing flexible modification in the polymer backbone [44,71,72]. Further, salicylic acid based PAs are a typical example of polymer therapeutics in which salicylates are released to produce anti-inflammatory action [42,73,74].

Other modifications of PA include poly(anhydride-esters), which include two different types of hydrolytically cleavable bonds in the polymer backbone, ester and anhydride. In a study, low molecular weight carboxylic acid terminated prepolymers of poly(ε-caprolactone) were coupled via anhydride linkages and, in another example, PLA was coupled with PSA to form triblock copolymer (PLA–PSA–PLA) for their use as stereocomplex based drug delivery carriers [75].

5. Polyanhydrides in clinical practice

5.1 Gliadel®

Brain tumors represent one of the most devastating forms of illness and the number of incidences occurring requires significant attention in the management of the disease. In the USA alone, primary malignant brain and central nervous system tumors affect approximately 18,500 persons each year with an incidence rate of 7.4/100,000 person/year The worldwide incidence rate of primary malignant brain and central nervous system tumors (age-adjusted using the world standard population) is 3.7 per 100,000 person/year in males and 2.6 per 100,000 person/year in females. The incidence rates are higher in more developed countries (males: 5.8 per 100,000 person/year; females: 4.1 per 100,000 person/year) than in less developed countries (males: 3.0 per 100,000 person-years; females: 2.1 per 100,000 person/year) [76]. More than three-quarters of these primary tumors are malignant gliomas. A typical glioblastoma grows rapidly and by the time it causes symptoms, the volume of the tumor is already life-threatening [77]. Conventionally, the treatment of gliomas includes diagnosis by biopsy and then resection of the tumors that are accessible without damaging the brain, followed by radiation and chemotherapy [78-81]. Despite advances in neuroradiology and neurosurgical technique, long-term patient survival has not been extended; the median survival after surgical resection alone is 6 months with only 7.5% of patients surviving 2 years. Additional radiation therapy extends the survival time to 9 months, while systemic chemotherapy has been minimally effective [82,83]. 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 [18]. This entails alternative approaches which may involve breaching BBB or modification of the drug molecule itself, both of which are not very feasible or rational approaches in terms of side effects and time consumed. Hence localized therapy resolves the problems associated with delivery of anticancer drugs as described earlier, particularly in the case of 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 molar ratio) is utilized for controlled delivery of BCNU in the form of Gliadel which is a sterile, off-white to pale yellow wafer with a diameter of 1.45 cm and 1 mm thickness. Each wafer contains 192.3 mg of a biodegradable PA copolymer and 7.7 mg of BCNU [84]. A battery of *in vitro* testing have been carried out to elucidate the degradation mechanism of polymer P(CPP:SA) and drug release from the system at various loading levels [26,85,86]. 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 [87]. Furthermore, as the surgical cavity was covered with BCNU polymer, the target cells were exposed directly to the therapeutic agent. From a market perspective, Gliadel was commercially launched in the USA by Rhône-Poulenc Rorer Pharmaceuticals (RPR) in February 1997.

Preclinical and clinical studies suggest an improved safety and efficacy profile of Gliadel over conventional systemic delivery of BCNU. In preclinical studies, the efficacy of Gliadel was evaluated in terms of the concentration of the drug achieved in local and systemic compartments followed by testing in disease models. Tritiated BCNU was used to access its biodistribution via Gliadel as well as after direct stereotactic injection [88]. Quantitative autoradiography of the brain sections of animals killed at various time points revealed that in the case of Gliadel approximately 50% of

the ipsilateral hemisphere was exposed to BCNU at day 3, and 10% was exposed at day 14. A wafer containing 600 mg of BCNU produced tissue concentrations of 6 mM at 10 mm from the implantation site on both day 3 and day 7 after implantation. Direct injection, in contrast, showed an initial high concentration of broadly distributed BCNU at 1 and 3 h post-injection, which then rapidly disappeared. A further study with 20% (w/w) BCNU loaded P(CPP:SA) polymers in monkeys found tumoricidal concentrations of BCNU at 4 cm from the implant site at 24 h post-implantation [89]. The preclinical data revealed local, sustained, clinically significant levels of BCNU via Gliadel to neural tissue *in vivo*.

The efficacy of Gliadel was checked in a rat flank and intracranial 9L gliosarcoma model and it was found that survival of the animal had increased 5.4-fold and significantly less, 2.4-fold, with respect to control in the case of Gliadel and systemic therapy respectively [90]. In an another study, Buahin and Brem demonstrated the advantage of controlled delivery via Gliadel over localized free-drug injection where median survival improved 271% as compared to 36% for in the direct injection group [91]. Ratio of CPP to SA and loading of BCNU was also optimized by comparing *in vitro* release and efficacy testing in rat intracranial 9L gliosarcoma model at different levels [92]. At lower concentrations, 50:50 and 20:80 ratio showed no disparity in release whereas at higher loading of BCNU, release was slower in the case of 50:50. In efficacy testing, survival was 20% in BCNU loaded PCPP:SA (20:80), the formulation rendered 63% survival at 200 days, whereas median survival in the control (polymer treated) group was < 20 days. Moreover, no systemic side effects were observed due to polymer. Further, MRI images revealed the absence of edema or any other gross adverse effects at the site of implantation. Finally, delivery of various antineoplastic drugs including BCNU via P(CPP:SA) (20:80) polymer was carried out in a rat model with different type of cancer cells (tumor lines) with and without concurrent radiation therapy to elucidate the best combination for the treatment [91,93]. On the basis of the results from these preclinical studies, which had proven the safety and efficacy of Gliadel in terms of polymer as well as improvement over conventional systemic therapy, clinical studies were initiated using PCCP:SA (20:80) loaded with BCNU.

Initially, Phase I–II studies were carried out in patients with recurrent malignant gliomas and failure of standard treatment which required reoperation [87]. Twenty-one patients were treated, and three different polymer loads were tested: 1.93, 3.85 and 6.35% (w/w). Each device weighed 200 mg, and most patients received a maximum of eight wafers implanted within the tumor cavity following debulking. Tumor volumes were similar in all groups. No evidence of systemic and bone marrow toxicity was observed in regular evaluations. The implants were visible in MRI and CT scans up to 49 days. The overall median survival times were 46 weeks after implantation and 87 weeks after initial diagnosis, with 86% of patients alive after more than 1 year of diagnosis. Based on this clinical trial, the 3.85% BCNU-loaded polymer was eventually chosen for further clinical study. After successful completion of the Phase I – II study, a more scrupulous Phase III study was carried out which was multi-centered, prospective, randomized, double-blinded and placebo-controlled [94]. Two hundred and twenty-two patients were included in the study at 27 medical centers in North America, with inclusion criteria similar to the Phase I–II study. Patients were randomized to receive either the BCNU polymer or a blank placebo. All patients had received external beam radiotherapy and 52.7% of the BCNU–polymer group and 48.2% of the control group had chemotherapy. The median post-operative survival of the patients implanted with BCNU-loaded polymer was 34 weeks compared to 23 weeks in the placebo group. The 6-month survival rate was 60% in the treatment group, and 47% in the placebo group. More significant improvement was found in glioblastoma patients (n = 145), where there was a 50% increase in 6-month survival with BCNU-loaded PA compared to placebo treatment ($p = 0.02$). Similar to the Phase I – II, study no systemic or bone marrow toxicity was reported. The BCNU–polymer group has shown some local infection which, however, was not clinically significant and even post-mortem reports showed a mild inflammatory reaction. Consequent to the successful completion of this Phase III study, the FDA in 1996 approved 3.85% BCNU-loaded PCPP:SA polymer (Gliadel) for the treatment of recurrent glioblastoma multiforme. Gliadel was then tested for its use after initial surgery (as initial therapy) in Phase I, II and III trials where a similar safety and efficacy profile was found. In these cases, Phase III patients were followed for up to 3 years, which indicated that long-term survival was increased in patients with local (implanted) chemotherapy [95]. A small, randomized Phase III trial in 32 patients undergoing initial resection for malignant glioma was carried out [96]. The proportion of patients surviving at 2 years was 31% in the BCNU wafer group compared to 6% in the group treated with placebo wafers. This benefit remained at 3 years, with 25% still alive in the BCNU wafer group as compared to 6% in the placebo wafer group. Overall, patients treated with BCNU wafers (n = 16) had a 73% reduction in the risk of death ($p = 0.006$) compared with placebo. Recently, Westphal and colleagues [97] conducted a trial enrolling 240 patients to confirm the Gliadel advantage in a large population. Year-wise survival of the patients treated with Gliadel and placebo is given in **Figure 3**. A significant 27% reduction in the risk was observed and the survival advantage was maintained at 1, 2, and 3 years and was statistically significant ($p = 0.01$) at 3 years.

5.2 Septacin™

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 supplied

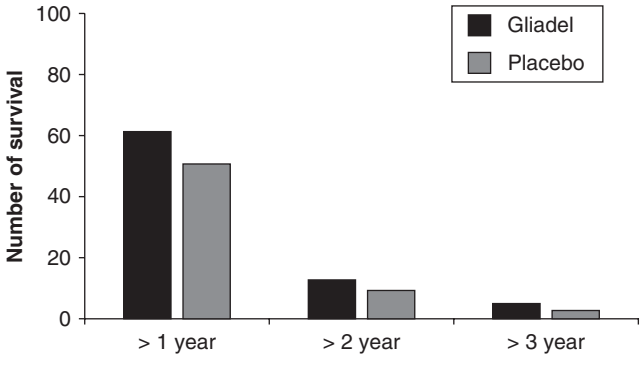


Figure 3. Year-wise survival of the patient treated with Gliadel® and placebo. A statistically significant difference in the treatments was found. The total number of patients initially was 240.

as strands, each of which has five beads with linkers. Each bead is 12 mm long and 4 mm in diameter and weighs around 150 mg, containing 20 mg gentamicin as gentamicin sulfate. Matrix is prepared by melt mixing procedure and injection molding machines are used for further processing. Large-scale production is carried out on automated machines, which include twin-screw extruder, gravimatric feeders, cooling conveyers, pelletizer and production-scale injection molding machine. The product is packed in plastic blister and finally sealed in aluminum stir pans. Sterilization is done by γ-radiation [98]. Stephens *et al.* 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 [99]. 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.* [100,101]. In water, the release of drug was faster than the copolymer erosion, indicating that the drug hydrophilicity and its diffusion through the cracked matrix structure play a critical role. Release in pH 7.4 buffer was found to be diffusion controlled. The beads did not crack and were observed to swell over the course of the experiment. Osmotic effects of the dissolution medium were found to be minimal. Amide formation between the drug and the copolymer was also considered. Amides were forced to form between gentamicin and PSA. However, no amide formation was observed between gentamicin and the EAD:SA copolymer. Sulfate ion exchange was observed during drug release at pH 7.4, indicating that a salt may be formed between gentamicin and monomer (or oligomers) in the degraded copolymer matrix. Additional data on the salt formation between gentamicin and EAD further supports the conclusion that the slow release of gentamicin from Septacin in pH 7.4 buffer was attributed to the formation of insoluble salt of gentamicin and EAD monomer (or oligomers) in the copolymer matrix [102,103]. These results indicated that the relationship between the drug and the polymer could play a critical role in the *in vitro* release characteristics. In addition, cationic drugs have the potential to form hydrophobic salts with monomeric (or oligomeric) hydrolysis products of PAs. These salts can radically affect the *in vitro* release profile.

For *in vivo* evaluation, initially pharmacokinetic study was performed by implanting either one or three Septacin beads in the back of Sprague–Dawley rats. The release was followed for 6 weeks post-implantation and gentamicin release was almost over by the fourth week. Plasma levels were found to be minimum and moreover no difference in plasma profile of one and three beads was observed after 2 weeks, which clearly indicates the benefit of localized drug delivery [98]. The *in vivo* profile was found to be mimicking the *in vitro* profile in water rather than in buffer (pH 7.4). The efficacy of Septacin was preclinically evaluated in rat skin abscess model wherein the subcutaneous tissue was inoculated with *Staphylococcus aureus* and treatment was given in the form of subcutaneous implantation of Septacin beads at different distances (1 – 2, 2 – 4 or 4 – 6 cm) from the infection site. This study revealed that the distance between the placed implant and diseased site is very critical; the shorter the distance, the better the therepeutic effect and this is due to localized drug release from the implant [98]. Further, efficacy was determined in a group of six horses with *Staphylococcus aureus* infected tarsocrural joints. One day after infection, two sets of seven Septacin beads were separately placed into the dorsal and the plantar pouches of the infected joint. The same number of beads was placed in the dorsal and plantar pouches of the contralateral joint. Treatment significantly improved the joint infection, joint synovitis and eliminated infection in one-third of joints within 3 days and two-thirds of joints within 13 days. In the non-infected joints, Septacin beads produced a mild-to-moderate synovitis over 13 days but did not produce detectable clinical lameness or evidence of joint pain [98].

Trial in humans was done with subjects who were undergoing surgical removal of infected prosthetic hip or knee joints. The patients were implanted with Septacin beads equivalent to 100 – 800 mg gentamicin (5 – 40 beads) with simultaneous treatment of i.v. antibiotics other than gentamicin. The wounds were catheterized and wound drainage was collected and extremely high local gentamicin concentrations, which appear to correlate with the total dose of beads implanted, were found. If the same concentration was achieved by a systemic dose, it could cause serious otic toxicity, therefore the use of Septacin can be of great advantage. Moreover, no measurable systemic levels of gentamicin

(LOD 50.27 μg/ml) were detected. The study again proved the advantage of localized delivery in delivering drugs with high systemic side effects [98].

6. Polyanhydrides under development

Since the pioneering work by Langer in the 1980s, PAs have been investigated extensively for application in various biomedical fields. Compilations of all the research work on various types of PAs have been made in the form of reports and reviews [25,29,104-106]. Developments are still taking place and various types or subtypes of polymer have been discovered in the recent past. Thus, we will focus on new PAs reported and explored in the last five years which are intended for use in drug delivery or other biomedical applications. Critical structures of new polyanhydride classes are depicted in **Table 1**. 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 based;
- salicylate based; and
- succinic acid based.

6.1 Amino acid based polyanhydrides

Amino acid based PAs were first reported in the 1990s by Domb [107], however, recent progress in this class has been made in terms of producing crosslinked PA which are suitable for *in vivo* use [39,69]. Previously, alanine containing crosslinked PAs in which linkages were produced by irradiation of methacrylated end groups which when hydrolyzed give rise to non-biodegradable products having limited biocompatibility. To overcome these limitations, crosslinked amino acid PAs were produced having exclusively anhydride bonds which are hydrolabile in nature. Crosslinked amino acid-containing PAs based on *N*-trimellitylimido-β-alanine (TMA-ala) or *N*-trimellitylimido-glycine (TMA-gly) and sebacic acid (SA) were synthesized by copolycondensation using 1,3,5-benzenetricarboxylic acid (BTC) prepolymer as a crosslinking agent (**Figure 4**). Crosslinking was confirmed by single melting peak of the polymer in differential thermal calorimetry studies [69]. Monomeric SA prepolymer was prepared to prevent phase separation and produce homogeneous polymeric matrix. *p*-nitroaniline was incorporated in the polymer matrix by compression-molding in the form of a disc. They were then placed in buffer (0.1 M, 7.4 pH) and the release of *p*-nitroaniline as well as TMA-gly was measured and found to be similar to its linear counterpart of the polymer (TMA-gly:SA 30:70) [70,108], indicating that crosslinking has little effect on the degradation behavior of this particular polymer, possibly due to its high hydrophilicity and low degree of crosslinking. Thus, the system gives opportunity to further evaluate the degree of crosslinking and control over the same to produce material useful for varied application.

In another study by Zhang *et al.* [40], the effect of the type of amide bonds present in the PA backbone and its blending with polyesters like PLA on degradation has also been studied. *N,N′-bis*(L-alanine)-sebacoylamide (BSAM) and its polymer, P[1,6-*bis*(P-carboxyphenoxy) hexane (CPH)-BSAM] were synthesized and blended with PLA. Hydrolytic degradation of PAs and their blends with PLA were evaluated in 0.1 M phosphate buffer pH 7.4 at 37°C. The results indicate that the existence of amide bonds in the main chain of polymers slow down the degradation rate, and this tendency increases with the increasing amount of amide bonds. The copolymers and their blends with PLA possess excellent physical and mechanical properties, thus making them more widely used in drug delivery and nerve regeneration.

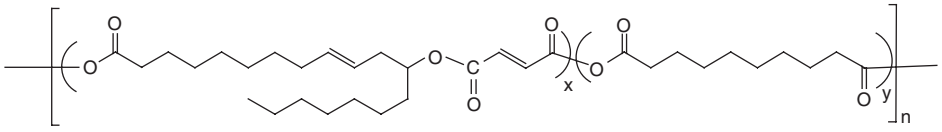
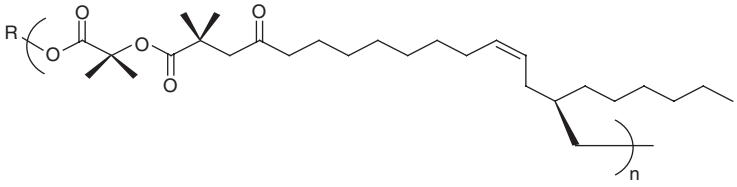
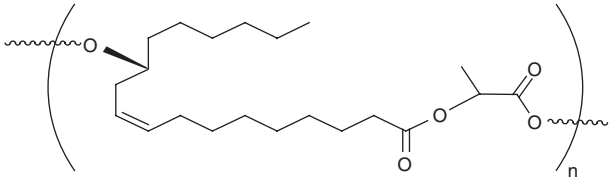
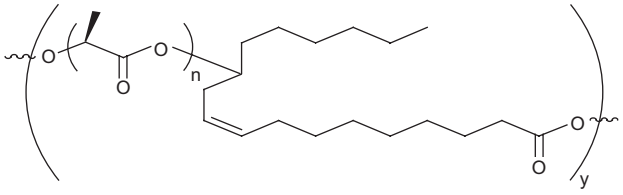
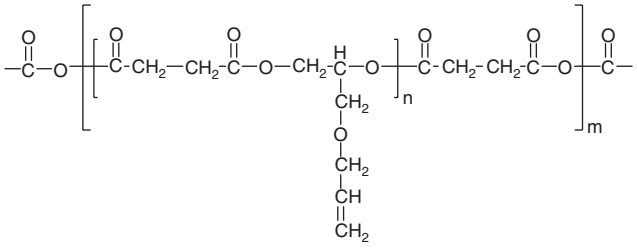
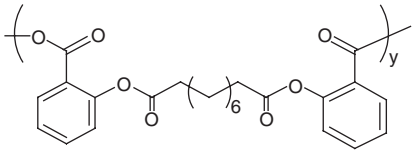
6.2 Photo-polymerizable polyanhydrides

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 advantages of photo-initiated polymerizations over other crosslinking techniques are 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. Ease of fashioning and flexibility during implantation in terms of physical and mechanical properties of materials without major modifications to the backbone chemistry, which can alter biocompatibility, is an added advantage. Apart from this, lack of availability of biocompatible monomers that form photo-polymerized polymer put a limitation on their extensive use in biotechnology and medicine [109,110].

Anhydride monomers with reactive methacrylate 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 [111].

Shastri *et al.* have prepared a new family of photochemically cured poly(anhydrides) (PA) which can produce semi-interpenetrating (semi-IPN) degradable networks, and evaluated them for biocompatibility in subcutaneous tissue in rats. These systems appear to undergo degradation primarily by surface erosion. They observed that the inflammatory response to these implants was minimal at both short (3 and 6 weeks) and long (28 weeks) time points. Furthermore, the fibrotic response was largely absent throughout the duration of this study. For reference, linear PA controls were tested and showed a foreign body response culminating in the formation of a relatively avascular fibrous capsule several cell layers thick, which became thicker over time, a response similar to what is typically observed in FDA approved implantable polymeric device systems [112].

Table 1. Chemical structure of new polyanhydride classes.

Polymer	Structure	Ref.
RA based		
Polyanhydrides		[27,33]
Copolyesters	(a) Ring opening polymerization using RA lactones (P(RA:LA)) 	[34,68]
	(b) Transesterification (P(RA:LA)) 	
	(c) Melt condensation (P(RA:LA)) 	
Succinic acid functional polymers		[43,44]
Amino acid based crosslinked polyanhydrides (with anhydride linkages only)	Crosslinked polymer of *N*-trimellitylimido-amino acid and sebacic acid (SA) using 1,3,5-benzenetricarboxylic acid (BTC) as crosslinker (**Figure 4**)	[39]
Salicylate based		[41]

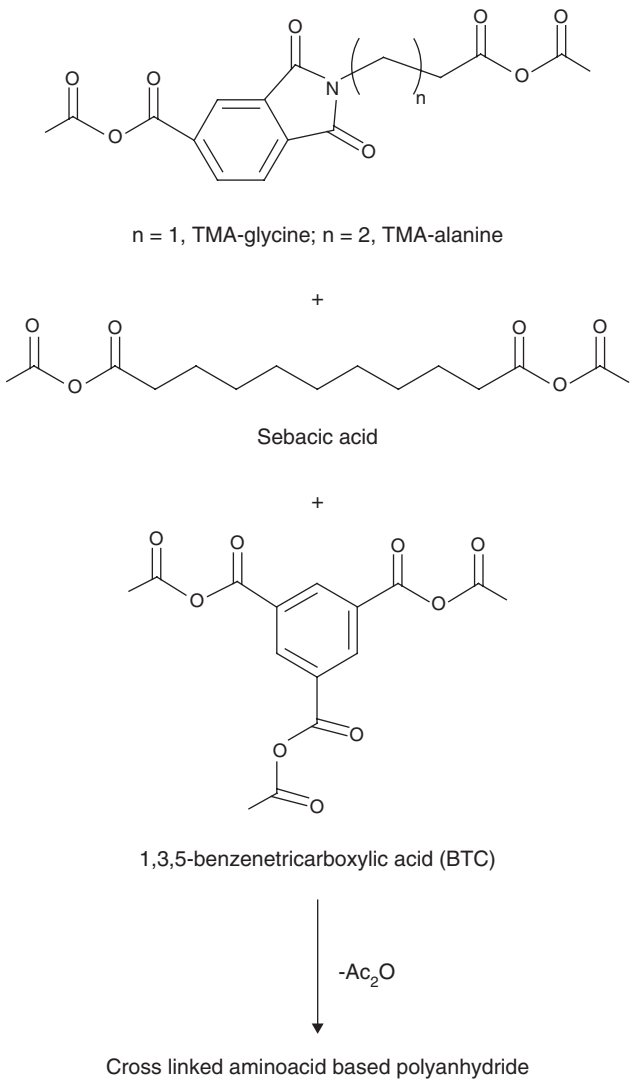


Figure 4. Synthesis scheme for crosslinked, amino acid based polyanhydrides using BTC as a crosslinking agent.

In an another study, Poshusta *et al.* examined cell–polymer interactions in subcutaneous and bony tissue after implantation of *in situ* forming and surface eroding photopolymerized disks of several PA compositions in rats. Varied histological responses were observed depending on the degrading polymer composition. It was shown that 50/50 poly(MSA)/poly(CPP:CPH) showed a cellular response that was similar to poly(lactic acid) controls. A model defect created in the proximal tibia was used to assess the effect of photopolymerization reaction on local bony tissue. At 7 days, new bone spicules in the fibrous callous were found to be present which indicated healing of the polymer-treated defect with no adverse effects from the photopolymerization reaction [110].

Weiner *et al.* have recently evaluated the potential of photo-crosslinked PA networks as an injectable delivery system for sustained release of bioactive molecules. Crosslinked networks composed of sebacic acid dimethacrylate (MSA), 1,6-*bis*-carboxyphenoxyhexane dimethacrylate (MCPH), and poly(ethylene glycol) diacrylate (PEGDA), supplemented with calcium carbonate, were examined for *in vitro* release of two model proteins (horseradish peroxidase (HRP) and bovine serum albumin labeled with fluorescein isothiocyanate (FITC-BSA). Release of protein ranging from 1 week to 4 months was achieved. In general, a more hydrophobic network resulted in slower rates of protein release. These results suggest that this system may be useful as an injectable delivery system for the long-term delivery of macromolecules [113].

6.3 Ricinoleic acid (RA) based polyanhydrides

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 [114]. RA (*cis*-12-hydroxyoctadeca-9-eonoic acid) was found to be the most appropriate alternative for the synthesis of the fatty acid based PAs. It is one of the few commercially available fatty acids that has the additional 12-hydroxy group. The advantage of RA is that it is a bifunctional fatty acid containing a hydroxyl group along the acid group and, therefore, can be incorporated into the PA backbone by the formation of an ester bond.

RA-based polymers are the newest addition to the PA series and were first investigated in the late 1990s [33]. However, the polymers produced were for solid implant, which need surgical intervention for application to the body system. Recent work is more focused upon converting this solid form to a liquid injectable form, which can form solid or semisolid implant after administration by injection [33]. For this, a first series of efforts were made with SA as the other monomer and this also included two subtypes: one is the insertion of ricinoleic acid in preformed SA chains [115]; and the second is the usual melt condensation carried out at a lower temperature in one-pot synthesis where dicarboxylic acid derivative of RA and SA are condensed together to from random copolymer rather than block copolymer [27]. Both of these efforts lead to the formation of polymers in a liquid injectable state. Although the common physicochemical properties such as low melting point, hydrophobicity, flexibility, biocompatibility and biodegradability desired for a drug carrier are possessed by all RA-based PA, the liquid state was achieved only with the polymer having more than 70% RA content.

Low molecular weight polymer synthesized by the one-pot, low temperature condensation method has led to the release of anticancer drug, methotrexate, for around 10 days (**Figure 5**) [27]. It was observed that a change in RAM (RA maleate) ratio in RAM-SA polymer affected the drug release, which was higher at higher concentrations of RAM,

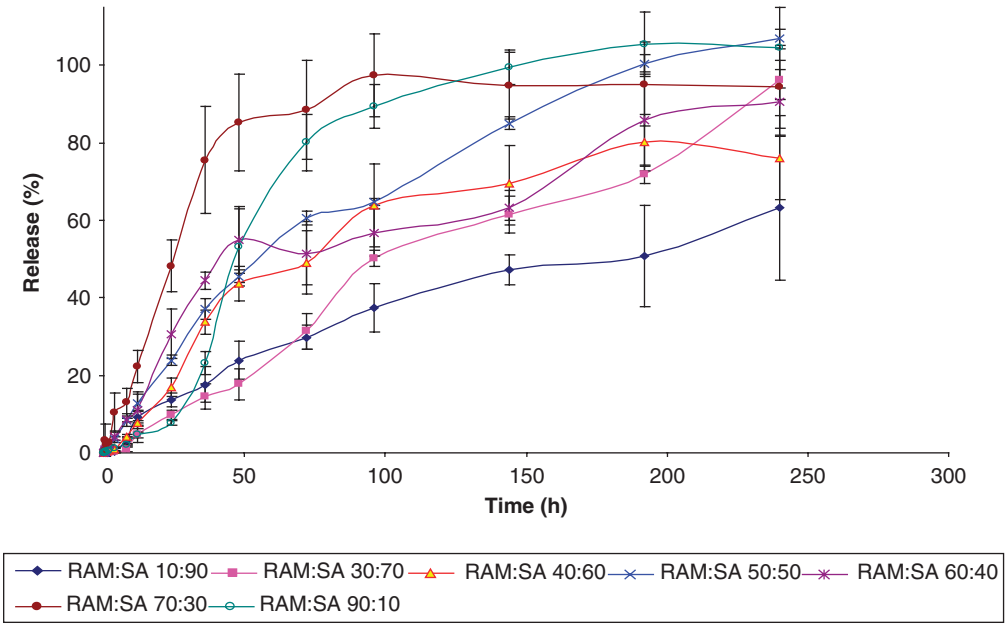


Figure 5. MTX (5% w/w) release from low molecular weight, one-pot P(RAM:SA).

and this was due to a decrease in polymer crystallinity. A high decrease in crystalline behavior of polymer overrode the hydrophobicity of RAM which results in higher drug release [33]. Similar results were found in polymers obtained by the insertion of RA in the SA chain [67,115] where these polymers were loaded with cisplatin (5% w/w) and paclitaxel (5 – 20% w/w) and drug release was faster with the pasty polymers. *In vivo* evaluation of bupivacaine loaded P(SA:RA)(2:8) injectable polymer was made in terms of efficacy and toxicity for producing motor and sensory block when injected near the sciatic nerve [66]. A single injection of 10% bupivacaine in the polymer caused motor and sensory block that lasted 30 h without causing any adverse effects.

In a second series of polymers, sol-gel reversible phenomenon was ramified in the form of RA copolyesters. In one study, ricinoleic lactone were utilized for the synthesis of copolyester by ring opening polymerization (ROP) [68]. RA lactones were synthesized by using dicyclohexylcarbodimide and (dimethylamino)pyridine as catalyst. Various macrolactones were obtained, mono- to haxa-lactone depending on the number of RA moieties which participate in the lactone ring formation. Polymerization of the ricinoleic acid lactones with catalysts commonly used for ring-opening polymerization of lactones, under specific reaction conditions, resulted in oligomers. Polymerization of chromatography-purified dilactone with $Sn(Oct)_2$ resulted in the formation of longer oligomers (weight average MW = 5700). However, copolymerization with lactide resulted in copolymers of low molecular weight. Polymers with molecular weights in the range 5000 – 16,000 were obtained with melting temperatures of 100 – 130°C for copolymers containing 10 – 50% w/w ricinoleic acid residues. The polymers were off-white in color, becoming yellow with an increase of the RA content. The molecular weights of the polymers decreased with an increase in the content of the ricinoleic acid lactone. It was hypothesized that more reactive lactide activated first by catalyst polymerizes and only in the end do some ricinoleic acid lactones react. The reaction was terminated because of the ricinoleic acid lactones' low reactivity. This low reactivity can be attributed to the low ring strain and to the steric hindrance of the ester bond by the fatty acid side chain. *In vitro* degradation of RA–LA copolymers showed that copolymerization with RA had some effect on the degradation rate and the polymer physical properties, which are related to the low incorporation of RA in the polymer. The addition of ricinoleic acid (RA) to poly(lactic acid) (PLA) is expected to improve the hydrophobicity of the polymer and thus the drug release profile.

In continuation of the above study, synthesis methods other than ROP, such as transesterification and melt condensation were also utilized (**Figure 6**) [34]. The liquid state of polymer which makes it a potential candidate for directly injectable drug delivery carrier was achieved when RA content increased more than 15 and 50% in case of melt condensation and transesterfication, respectively.

Polymers synthesized by all three methods were compared for release of hydrophilic and hydrophobic drug viz. 5-FU and triamcinolone respectively. 5-FU release was faster in all cases, with the total release lasting for 17 days from polymers prepared by transesterification and melt condensation.

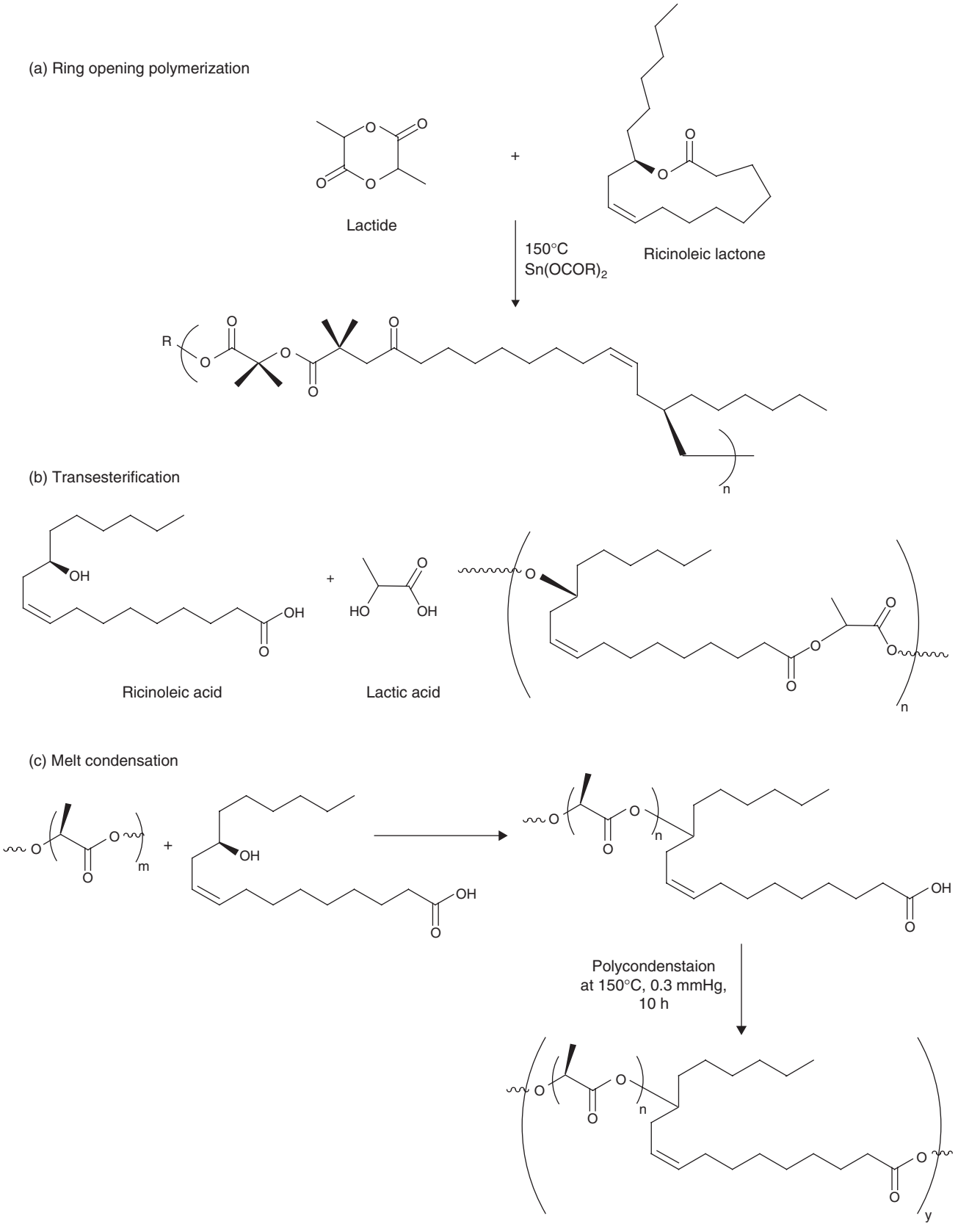


Figure 6. Synthesis of RA-based copolyesters by various methods.

Slower 5-FU release was obtained from polymers prepared by ROP (40% in 17 days). The same pattern was observed for triamcinolone, where the release was obtained was only 5% in 17 days from ROP polymer in contrast to 30% from polymer synthesized by transesterification. The difference was attributed to the diblock nature of ROP polymer, its high crystallinity and melting point, all of which inhibit water penetration and thus degradation, which finally shows up in release profiles [34].

6.4 Salicylate-based polyanhydrides

Erdmann *et al.* [42] reported on salicylic acid based polymers in 2000 and these have then been investigated extensively over the last few years. These salicylate-based poly(anhydride-esters) were 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 wherein the drug (salicylate derivative) is an integrated part of the polymer backbone. Aminosalicylic acid is a useful bioactive agent for inflammatory bowel disease and the drug needs to be specifically delivered at the site of action, that is the colon. Synthesis of this category of polymers can be carried out by the usual preparation of prepolymers and then melt condensation to produce high molecular weight polymers [41], however, for this the synthesis method has been modified by Schmeltzer *et al.* wherein the reaction conditions and even condensation reactor was modified to include dynamic mixing of the reactant to yield high molecular weight polymer [116]. The reaction was further modified to a more mild form wherein PA drugs with glass transition temperature 35.7 – 44.0°C were prepared by reaction of salicylic acid or diflunisal with C10-18 diacid chlorides in the presence of a base [117]. Polymerization of the diacid intermediate was carried out in the presence of base and a coupling agent. This class of polymers has also been synthesized using various salicylic acid derivatives like halogenated salicylates, aminosalicylates, salicylsalicylic acid and thiolsalicylic acid [118]. The poly(anhydride esters) were synthesized by melt condensation polymerization. The halogenated salicylate derivatives yielded the highest molecular weight polymers as well as the highest glass transition temperatures. All these derivate polymers displayed *in vitro* degradation lag times from 1 to 3 days, depending on the water solubility of the salicylate derivative. In another example, PEG-based polymer such as poly[bi(o-carboxyphenyl)adipate-polyethylene glycol] anhydrides-P(BOCA-PEG) was synthesized with salicylic acid loading of 43.5 – 71.3%, which was much higher than other polymers of this class [119]. Polymers with 4- and 5-aminisalcylic acid were found to degrade at temperatures above 100°C. The polymers were found to degrade completely at pH 7.4, however, almost 50% of mass remained even after 90 days incubation at pH 1.2, hence they were suitable for delivery of amino salicylic acid (ASA) specifically to the site of higher pH, which is the colon. Another novel PA poly[(5-carboxybutylformamide)-2-acetylsalicylicanhydride] (P(CBFAS)) was synthesized containing 5-ASA in the backbone and was studied in terms of factors affecting 5-ASA or its acetyl derivative [73]. The results showed that the release rate of 5-ASA and 5-acetyl ASA increases with increasing pH value and with decreasing molecular weights. Enzymes including pepsin and trypsin, as well as rat gastric and jejunum contents, had little effect on the release rate. However, the release rate was much faster in PBS (pH 8.0) containing 5% of cecal contents. Considering the high drug loading of the polymer (50.2% of 5-ASA moieties in the backbones) and the degradation characteristics, it is possible to reach high local concentration of 5-ASA in the colon site via oral administration. Therefore, P(CBFAS) may be potentially useful in the colon-specific delivery of 5-ASA. PEG-based polymers also shown similar effects in the response to the presence of cecal content on the release of salicylic acid and increase in PEG, which is hydrophilic in nature, also increased the release rate [119]. Salicylic acid based poly(ester-anhydride) have also been tested for healing of long bone defects in rats with 5-mm mid-diaphyseal defects in femurs. Microspheres of the polymer were packed into the defect and compared with collagen sponge for reduction in bone loss. Although initially there was no significant reduction in bone loss, after 8 weeks a significant reduction in the bone weight loss was observed in the polymer group [120]. In another study, polymers prepared from salicylic acid derivative were evaluated for cytotoxicity using L929 fibroblast cells in serum-containing medium on parameters like cell viability, proliferation and morphology and these were found to be normal for most of the polymers evaluated [118].

In a further example, salicylic acid is generated as a metabolic product of poly-(anhydride-esters), that is copolymers of poly(1,10-*bis*(o-carboxyphenoxy)decanoate) (CPD) and poly(1,6-*bis*(p-carboxyphenoxy)hexane) (p-CPH). CPD degrades to salicylic acid and increase in its content in the copolymer, although it resulted in higher loading of salicylic acid, also leads to thermal and mechanical instability [74].

All salicylate-based polymers degrade to produce salicylic acid and all of these were found to follow primarily surface erosion patterns [121]. Furthermore, the effect of media on degradation rate was studied and found to increase marginally (14%) in media containing actively growing bacterial culture than sterile media. A significant reduction in formation of *Pseudomonas aeruginosa* biofilm in a long-term (3-day) study with the salicylic acid containing polymers was demonstrated and pathway was postulated using *P. aeruginosa* pMHLAS, containing a fluorescent reporter gene and found to be inhibition of the las quorum sensing system [122].

6.5 Succinic acid based polyanhydrides

Succinic acid is one of the naturally occurring substances of living tissues, and polymers prepared using this acid can be inherently biodegradable and biocompatible.

Inclusion of succinic acid in the polymer chain has been made for various functions. Initially, it was used to convert monocarboxylic monomer to dicarboxylic, as in the case of RA to help polymerization reaction [72,123,124]. In another case its chloride derivative (succinic chloride) was used to prepare fluorescent monomer with p-hydroxybenzoic acid which was further copolymerized with SA to form the polymer, which is fluorescent; particles made by the same polymer can be helpful in understanding their behavior in various biomedical applications [125]. Moreover, an increase in the ratio of fluorescence monomer led to a decrease in degradation rate which in turn can be useful in altering the release behavior. In earlier work, succinic acid was directly used as one of the monomer units for, for example Ben-Sabat *et al*. have synthesized copolyanhydrides from trimers of fumaric acid, succinic acid and propylene glycol [43]. These polymers were found to degrade and release the entrapped drug substance in a week's time and *in vivo* testing in rats proved the polymer safe for further investigations as a drug delivery carrier. Succinic acid derivatives were utilized more widely to synthesize unsaturated and functional polymers. Copolymers of 2-hexadecylsuccinic acid and sebacic acid were prepared using the usual melt condensation method and demonstrated to be a potential drug carrier for localized drug delivery [71]. In another study, hydroxyl group functional polylactones were prepared and converted to acid-terminated polyesters in a reaction with a series of alkenylsuccinic anhydrides containing 8, 12, or 18 carbons in their alkenyl chains [123]. These polyester units were then condensed in high molecular weight polymer. Polymer hydrolysis was found to decrease by the presence of alkenyl chain in case of low molecular weight precursors, but the converse was the case with polymers with high molecular weight prepolymers. There was no pronounced effect of differences in length of the alkenyl group on degradation rate. Recently, succinic acid based functional polymers have been synthesized with allyl pendent group, which can be utilized for further copolymerization or attachment of other moieties to perform specialized function [44].

Synthesis of these functional polymers was carried out in three steps; initially carboxyl terminated functional oligoesters with molecular weight 300 – 1000 Da were obtained by melt condensation of allyl glycidyl ether with an excess of succinic acid, then the macromere with carboxyl end obtained were converted to mixed anhydride groups by refluxing in acetic anhydride and finally melt polycondesation of ester–anhydride prepolymers was carried out to form the polymer. The influence of molecular weight of initial oligoesters as well as of parameters of the process on selected properties of poly (ester-anhydride)s was examined. The hydrolytic degradation was monitored by determination of mass loss and by determination of ester to anhydride groups ratio. These poly(ester-anhydride)s display a 2-phase degradation profile with an rapid initial degradation of anhydride bonds followed by a relatively slower degradation of oligoester.

7. Conclusion

In this article, various PAs have been discussed, with a major emphasis given to the use of these polymers as localized drug delivery systems. Due to the labile nature of anhydride bonds, these polymers are highly susceptible for hydrolysis and thus they has been utilized as surface erodible carriers in drug delivery. Due to their surface erosion properties, they also enjoy the benefit of close to zero order release systems and take advantage over other systems. Despite all these benefits, there are very few PAs that have reached the market, in the form of Gliadel and Septacin beads. In both these products, drug release was controlled with the hydrophobic and hydrophilic balance by controlling the hydrolytic degradation. There are few new PA-based systems: injectable recinoleic acid based PAs which are in the advanced stage of development to reach the market and could be important carriers for anticancer agents and for other drugs as a depot for controlled drug delivery over a period of time.

8. Expert opinion

In drug delivery, a good carrier is an important part of the system that can hold, protect and release the drug molecule at our desired discretion. In general, a matrix system follows diffusion-based release, which is dependent on the initial concentration loaded in the devices and hence does not follow the zero order release profile, which is a gold standard in any drug release system. Polyanhydrides as a surface erodible system controlled the release by controlling the degradation of the polymer, hence their release is not dependent on the initial drug loading of the system, and thus follow close to zero order release status. Along with such benefits, these polymers have been commercialized as implant-based systems which restrict their application due to the involvement of surgery during treatment. Due to this hurdle, this polymer class is under-utilized. Currently, research is ongoing into the development of injectable systems in the form of liquid polymers, which are low melting polymers and can be delivered via injection or in the form of injectable particulate PA systems which will open the gate as drug carrier to a variety of drugs.

Declaration of interest

The authors state no conflicts of interest and have received no payment in the preparation of this manuscript.

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