Recent research and development in synthetic polymer-based drug delivery systems

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In recent years, there has been increasing recognition that a number of synthetic polymers which have excellent biodegradability and biocompatibility are materials of pharmaceutical importance in the area of drug delivery technology. The aim of this review is to take a closer look at a few synthetic polymer-based drug delivery systems, specially the aliphatic polyesters, polyamides, polyethers, polyorthoesters, polyanhydrides, polyurethanes, hydrogels and dendritic polymers.

Keywords: drug delivery, biodegradable, biocompatible, synthetic polymers

1 Introduction

Controlled drug delivery technology[1-3] represents one of the emerging and challenging frontier areas of research in modern medication and pharmaceuticals. Controlled drug delivery systems aim to achieve more effective therapies which eliminates the potential for both under- and over-dosing originating from uncontrolled drug release and avoid the need for frequent dosing and target the drugs better to a specified area. Furthermore, this administering technology offers the advantages of maintaining the drug levels within a desired range, minimising the drug side effects through optimal use and increasing patient compliance. While the advantages of using controlled drug delivery can be significant, some specific problems cannot be ignored: the possible toxicity or nonbiocompatibility of the used materials, undesirable by-products of degradation, requirement of surgery to implant or remove the system, the chance of patient discomfort from the delivery device, and the expensiveness of controlled-release systems compared with traditional pharmaceutical formulations.

Obviously, the ideal drug delivery system should be inert, free of leachable impurities, biocompatible, mechanically strong, comfortable for the patient, capable of loading higher amount of drugs, safe from accidental release, simple to administer and remove, easy to fabricate and sterilise, and efficient drug targeting specificity. The drug delivery systems based on polymeric backbones fulfil the majority of these requirements and have come to the centre stage of biomaterials research in recent years. The article reviews the recent developments and utilization of biodegradable synthetic polymers with emphasis on polyesters, polyamides, polyethers, polyorthoesters, polyanhydrides, polyurethanes, hydrogels as well as dendritic polymers in the field of controlled drug delivery research.

2 Mechanism of polymer controlled drug release

There are three primary mechanisms involved in the controlled drug release systems: diffusion, degradation and swelling followed by diffusion.[4] Any or all of these mechanisms (Fig. 1) may occur in a given system. In a diffusion system, the drug is either encapsulated in a polymer membrane or suspended within a polymeric matrix. During the design of polymeric drug delivery devices employing diffusion, the parameters such as size of drug molecules, porosity of polymer matrix, degree of crosslinking and swelling characteristics of polymer play an important role. Polymer degradation is perhaps the most interesting method of drug release.

As with the diffusion method, the drug is contained within a polymeric membrane or matrix. The polymer is designed to degrade and release the drug at a specific location in the body.

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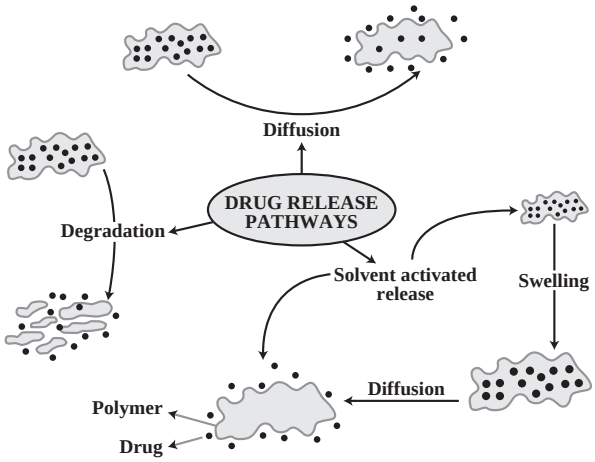


Fig. 1

As the polymer degrades, the drug is freed and made available to the body. The greatest advantage in using degradable polymers in controlled drug release systems is that they are broken down into biologically acceptable molecules that are metabolised and removed from the body via normal metabolic pathways. In this regard, responsive drug delivery[5] is another promising approach in which drug is released in a pulsed manner only when required in the body. In responsive drug delivery systems, the delivery matrix is coupled with a sensor that stimulates the drug release through the detection of the environmental parameters. A large body of work in this area has as its eventual goal insulin delivery to diabetic patients through the control of the release of insulin in response to increased blood glucose levels.[6] Glucose oxidase, immobilised in the delivery matrix, acts as the sensor and maintains the blood sugar levels on converting glucose into gluconic acid which in turn lowers the body's pH and directs insulin for release.

3 Biodegradablity of polymers

Recently, there has been much publicity on using biodegradable polymeric materials[7-8] for the controlled delivery of important drugs to overcome the burden of surgical risk of removing them. Moreover, biodegradable polymers that are susceptible to biodegradation to biologically acceptable molecules in the physiological environment can be considered as ideal for the controlled delivery of drugs. However, based on the available literature, the following rules of thumb can be suggested to assess the biodegradability of synthetic polymers. Proper variation of each of these factors allows researchers to adjust the rate of matrix degradation and subsequently control the rate of drug delivery.

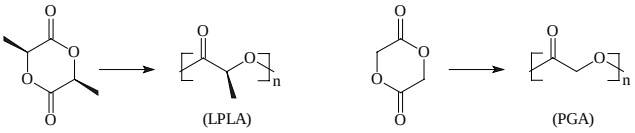
(i) More hydrophilic backbone chain – ester, ether, amide, peptide linkages improves biodegradation.
(ii) More hydrophilic end-groups – hydroxyl, carboxyl, carbonyl accelerate biodegradation.
(iii) Lower degree of crystallinity
(iv) Enhanced porosity
(v) Presence of lower molecular weight fraction
(vi) Geometry as related to size/shape and surface area.

4 Some synthetic polymer based drug delivery systems

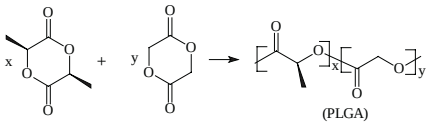
Over the last few years a variety of polymer-controlled drug delivery systems have been successfully developed for better therapeutic efficacy and better targeting of drug agents. Although a variety of approaches have been implemented for the utilisation of natural of synthetic polymer based drug delivery systems, we describe some of the biodegradable synthetic polymers that have been used.

4.1 Polyesters

Aliphatic polyesters are the most successful class of degradable polymers, used in drug delivery applications.[3,7] The degradation takes place via the hydrolysis of the ester linkages in the polymer backbone. Polylactide polymers (LPLA), polyglycolides (PGA) and their copolymers, poly(lactide-co-glycolide) (PLGA) are simplest biodegradable and biocompatible aliphatic polyesters of *L*-lactic acid, and glycolic acid. They are obtained through ring opening polymerisation of cyclic lactone and work well in the physiological environment during their controlled drug delivery applications.[9-11]

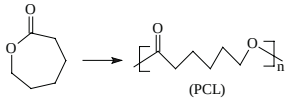


LPLA needs less time for biodegradation and yields acetic acid, a natural metabolite in the human body. Slower degradation of PLA derived from *D*- or *L*-lactide compared to racemic PLA is expected due to the higher order crystallinity of optically active forms.



However, Vert demonstrated[12] their degradation complexity depending upon the crystallinity (PGA>LPLA>PLGA) and the steric inhibition by pendent methyl group. Obviously, it would be highly desirable to have these polymeric materials with different rates of biodegradation and bioassimilation so that a clinician may select a proper matrix for delivery of drugs. Attempts has been made by various independent research groups to utilize these polymers for controlled drug delivery applications.[13,14] The design of plasticised, biodegradable polymeric materials, suitable for application as a drug delivery system, has been examined.[15] Racemic PLA oligomer was plasticised with 1,2-propylene glycol and glycerol. The latter plasticiser showed a poor compatibility whereas 1,2-propylene glycol was compatible with the polymer upto high concentrations. LeCorre and co-workers investigated[16] the *in vitro* cotrolled release of local anesthetics like bupivacaine, etidocaine, mepivacane and lidocaine from racemic PLA and PLGA microspheres. On a different front, another research group has successfully followed[17] the conjugation approach of drugs such as lysozyme and protected tryptophan to PLGA microsphere. Paclitaxel (Taxol) is one of the best antineoplastic drugs found from nature in the past decades. There are difficulties in its clinical administration due to its poor solubility. Therefore, an adjuvant has to be employed, but this has been found to cause serious side-effects. In this context, biodegradable PLGA nanoparticles containing vitamine E TPGS (d-ε-tocopheryl polyethylene glycol 1000 succinate) that have been recently reported by Mu and co-workers[18] can provide an ideal solution of adjuvant problem and provide a controlled as well as targeted delivery of drug with better efficacy and fewer side-effects.

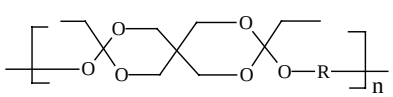
It is not surprising to note that most of the biocompatible as well as biodegradable aliphatic polyesters reported so far have been these polymers, since poly(ε-caprolactone) (PCL) obtainable from the ring opening polymerisation of ε-caprolactone is another widely used biodegradable and bioresorbable polymer for the sustained delivery of important drugs.[19,20]



This semi-crystalline polymer is permeable to low molecular weight drugs, non-toxic and its higher hydrophobicity compared with PLGA could be advantageous in oral immunisation. Furthermore, unlike PLA and PGA which generate acidic environments leading to irritation during their degradation, the delayed degradation characteristics of PCL do not generate an acidic environment during drug release. Moreover, PCL generates non-toxic and tissue-compatible products on degradation. These characteristics may thus help in planning its use for the sustained release of drugs, proteins, and vaccines. These potential advantages of PCL have increased its interest to a range of individuals engaged in both basic and clinical research in biomedical drug delivery science.[21,22] Recently, Merle and coworkers reported a facile way of encapsulation of vancomycin in bidegradable PCL microparticles for bone implantation. In their approach, encapsulation in the PCL microparticles (200 μm mean diameter) was most efficient using a simple solvent evaporation / extraction process that dispersed 122.5mg/g of polymer. Vancomycin was chosen because anti-staphylococcal treatment is sometimes required after bone surgery.

4.2 Poly(ortho esters) (POE)

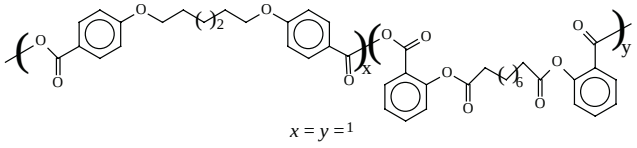
Poly(orthoesters) are another important group of hydrophobic polymer with drug delivery applications and which are synthesised by the addition of polyols to diketene acetals. POEs possess acid sensitive orthoester linkages that undergo a very slow rate of hydrolysis at the physiological pH (7.4). This increases at lower pH. Therefore, incorporation of small amount of acidic excipients is believed to control precisely the hydrolysis rate. On the other hand, incorporation of basic excipients stabilises the bulk of the matrix but facilitates erosion at the surface. Heller *et al*.[23] have extensively investigated the synthesis and application of the 3, 9-diethylidene-2,4,8,10-tetraoxaspiro[5,5]undecane (DETOSU)- based POEs derived from DETOSU monomer and diol.



Ng *et al*. reported[24] an elegant method for the synthesis of self-catalysed POEs having glycolide sequences that can be degraded hydrolytically without the help of catalyst excipients. Heller *et al*. also evaluated[25] the biotolerance of a semisolid hydrophobic biodegradable POEs for controlled drug delivery both in injections and the case of implant systems.

4.3 Polyanhydrides (PA)

Polyanhydrides[26] are useful bioabsorbable materials that have also shown promise as polymeric matrices in the field of controlled drug delivery. They are hydrophobic and contain water sensitive linkages undergoing hydrolytic bond cleavage to generate water-soluble degradation products. Surface erosion takes place due to water sensitive linkages. Their hydrophobicity, on the other hand, prevents the penetration of water into the bulk. These properties have been exploited to create a variety of new grades of polyanhydrides for controlled drug delivery applications.[3,27,28] The majority of PAs studied are based on sebacic acid(SA), *p*-(carboxyphenoxy)propane (CPP) and *p*-(carboxyphenoxy)hexane (CPH). The Sebacic acid component of biodegradable PAs is utilised as a surface eroding drug delivery device. A wide variety of drug and proteins have been incorporated into PAs and their modified forms *e.g.* poly(anhydride-esters), poly(anhydride-imides) *etc*. and their potential release characteristics have been evaluated.[29,30] PA based systems are currently under clinical development for the delivery of a powerful chemotherapy agent like BNCU in the treatment of brain cancer.[31,32] The agent, BCNU [1,3-bis-(2-chloroethyl)-1-nitrosourea], has a systemic half life of only 15min and when it is introduced into the body it exhibits various deleterious side effects. However, when the chemotherapeutic agent is incorporated into a properly designed PA polymer matrix, the release can be controlled so that a wafer implanted into the site of an excised tumor will release an effective flow of BCNU over a period of days or even weeks. Recently, Uhrich and co-workers have designed new type of poly(anhydride ester) incorporating sebacic acid and salicylic acid components.



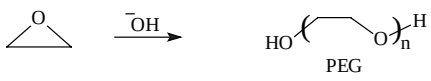
$x = y = 1$

Salicylic acid based poly(anhydride ester)

Salicylic acid is an antipyretic, anti-inflamatory analgesic with a half-life of 2–3h in low doses and upto 20h in high doses. Preliminary studies indicate that the degradation is controlled by the presence of the surface eroding characteristics of the sebacic acid component, producing a, localised reduction in inflammation as a function of polymer degradation.

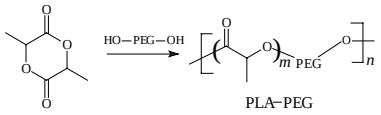
4.4 Poly(ethylene glycol) (PEG) based polymers

This is a hydroxyl group terminated linear polyether, synthesised via anionic ring opening polymerisation of ethylene oxide initiated by nucleophilic attack of hydroxide ion on the epoxide ring.



PEG

Researchers from the biomedical, biotechnical and pharmaceutical communities have become quite familiar with its excellent biocompatibility, non-toxicity, non-immunogenicity and water solubility facilitating its widespread use in many pharmaceutical and biotechnical applications.[33,34] PEGs have been extensively used as tablet formulation, crosslinked hydrogels and polymer drug conjugates. Copolymerisation with PLA is another promising strategy for use in drug delivery systems and tissue engineering.[35]



PLA–PEG

PEG part, incorporated in these copolymer systems imparts excellent beneficial surface properties within the body fluid. Since PEG contains terminal hydroxyl groups, further chemical manipulations like PEGylation of biological macromolecules are possible. This has been reviewed by Roberts *et al.*[36] Gref and co-workers described[37] the use of PEG-coated nanospheres from PLA, PGA or PCL for intravenous drug delivery in which the coated nanospheres may function as circulation depots for administered drugs. Silk protein polymers that are spun into fibers by silkworms have been used as biomedical materials for centuries. The biocompatibility of silk proteins may provide materials for use in the fields of controlled release and scaffolds for tissue engineering. In this regard, very recently, the blend film derived from two biocompatible polymers like *Bombyx mori* silk and PEG have been developed[38] and provide new potential tissue engineering scaffolds and controlled drug delivery.

Research interest in radiosensitisers is driven by the desire to destroy the malignant cells selectively in the presence of normal cells. The agent relies upon the selective increase of the lethal effect of radiation to the cancer cells with the least influence on normal tissues. Recently, Wang and co-workers have published a paper[39] describing the PEG modulated release of etanidazole radiosensitiser from implantable PLGA discs. Etanidazole, a second generation hypoxic cell radiosensitiser, is characterised by intracellular glutathione transferases inhibition, thereby enhancing sensitivity to radiation. In their work, etanidazole is encapsulated into spray dried PLGA microspheres and compressed into discs for controlled release applications. Incorporation of PEG can greatly enhance the release rate of discs and reduce the secondary burst effect, thereby achieving a sustained release for about two months.

4.5 Poly(amides)

Polyamides having structural resemblance to polypeptides are another important polymer used as matrices for the transport of drugs. Examples of such polymers include different types of poly(amino acids)[40-42] such as poly(L-glutamic acid), poly(aspartic acid) derived from the corresponding natural amino acids. The easy metabolism of poly(amino acids) into relatively non-toxic products reflects their good biocompatibility. Moreover, they are nonantigenic. The rate of degradation, however, can be controlled by a proper selection of the amino acid components. In view of their biodegradability as well as biocompatibility features, several groups of researchers have developed a variety of polyaminoacids and critically investigated their drug transporting capabilities. For example, Nakanishi and co-workers have developed[43] a polymeric micelle carrier system consisting of PEG-conjugated doxorubicin:poly(aspartic acid) for the transport of doxorubicin. This carrier system has a highly hydrophobic inner core, and therefore, it can entrap a sufficient amount of doxorubicin. Park and co-workers have investigated[44] the controlled release of clot-dissolving tissue-type plasminogen activator from a poly(L-glutamic acid) semi-interpenetrating polymer network hydrogel. The porous structure of a hydrogel is essential in this system to yield a large surface area so that tissue-type plasminogen activator release can be facilitated.

Very recently, Li and co-workers have synthesised[45] novel biodegradable poly(ester amide) derived from 3-morpholine and ε-caprolactone. The water absorption of polymers increases with increasing morpholine content. *In vitro* degradation data and release profiles of 5-fluorouracil showed that both the degradation rate and drug release rate increase with an enhanced morpholine content in the polymers.

4.6 Polyurethanes (PUs)

Polyurethanes form another important new class of polymers that can be considered to have both the structural characteristics of polyesters and polymides. PUs possessing the urethane linkages (–NHCO–O–) can be generated from the reaction between diisocyanates and diols as represented in the following scheme.

PU

Their susceptibility to biodegradation and excellent biocompatibility have motivated many researchers to consider their potential in biomedical applications.[46-48] For instance, Iskakov and co-workers have successfully prepared[49] the novel PU-based drug delivery systems with various antitumor drugs, such as cyclophosphane, thiophosphamide, vincristine and they have investigated their *in vitro* release characteristics. In another approach, PU-based drug release systems have also been reported[50] for the controlled release of chemotherapeutic agents like isoniazid, ethionamide, and fluorimicin for the prolonged treatment of the chronic microbial disease, tuberculosis.

4.7 Polymeric hydrogels

Hydrogels, three-dimensional polymer network capable of imbibing a large volume of water with significant retention of their three-dimensional structures after swelling, are another bio-related polymers the in the ongoing modern medical and pharmaceutical research. The gels should be degradable in order to avoid surgical removal of drug-depleted devices and degraded products should be biologically non-toxic. Because of the complex, three-dimensional giant hydrophilic structures, hydrogels are capable of absorbing aqueous solution and undergo degradation via erosion, hydrolysis, solubilization, and other biodegradation mechanisms.

A plethora of hydrophilic polymer backbones have been utilized as effective precursors for the development of hydrogels,[51-54] including PEG, poly(vinyl alcohol), poly(acrylic acid), poly(acrylamide), poly(N-isopropylacrylamide), dextran, gelatin, amylose, cellulose, chitosan, collagen, alginate, *etc*. Most of the designed hydrogel based drug delivery systems[55-58] respond to the local environment during release of drugs. For example, Peppas and co-workers have reported[59] the synthesis of a glucose-sensitive hydrogel that could be used to deliver insulin to diabetic patients by means of an internal pH trigger. This system possesses an insulin containing reservoir based on poly[methacrylic acid-g-poly(ethylene glycol)] hydrogel into which glucose oxidase has been immobilised. Immobilised glucose oxidase interacts with glucose and forces it to yield gluconic acid which in turn lowers the body's pH. This lowering of pH directs the insulin delivery and thereby maintains the sugar levels in the blood. Medical catheters are often coated with hydrogels to increase lubricity to aid insertion. This coating can also absorb therapeutic agents which can be released as needed during catheter use. Based on this encouraging issue, Gehrke and co-workers[60] have developed novel gel coatings and drug loading techniques which are optimised for drug delivery applications rather than lubricity. Very recently, Einerson and co-workers have successfully developed[60] novel hydrogels based on gelatin, ethylenediaminetetraacetic acid (EDTA) and PEG for drug carrier matrices. Zhuo and co-workers have prepared[61] the macro porous poly (N-isopropylacrylamide) hydrogels with high molecular weight PEGs for the controlled release of proteins.

4.8 Dendrimers

Dendrimers possessing unique structures and their properties have received considerable research interest in recent years. Their controllable highly branched, compartmentalised structures, size and associated surface properties are believed to make them suitable candidates for the construction of a variety of novel nanoscopic functional biomaterials. Additionally, their narrow molecular weight distribution facilitates uniform drug distribution and cellular uptake, easy processability, biodegradability, biocompatibility as well as the ability of the interior to encapsulate drug molecules show promise for their use as potential drug delivery systems.[62-64]

Additionally, dendrimers can carry the drug molecules in a manner in which the dendrimers serve as a hub onto which numbers of drug molecules can be attached via covalent bonding as depicted in Fig. 2.

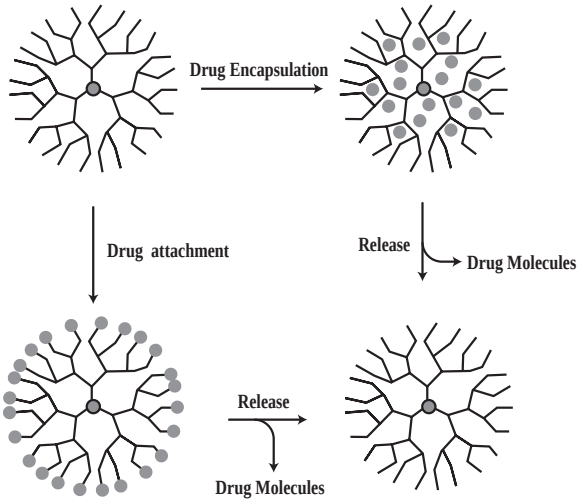


Fig. 2

The outcome of this approach is that a single dendrimer may transport a high density of drug molecules.

In this context, extensive reports on the use of biocompatible as well as biodegradable poly(amidoamine) (PAMAM) dendrimers,[65,66] first developed by Tomalia by utilising the repetitive sequence of Michael addition and amidation processes, as novel biomaterials such as drug encapsulation and release is impressive. Although, to date, these delivery systems remain largely unexplored, efforts have been made[67-69] to prepare dendrimers endcapped with biologically important PEG chains and showed that these modified dendrimers have the potential ability to retain anticancer drugs like adriamycin, and methotrexate.

Our experience of developing PAMAM dendritic diol indicated new routes of making biocompatible PAMAM side chain dendritic polyurethanes.[70,71] They are believed to provide good alternatives to the polymer controlled delivery of drugs. It is further anticipated that the introduction of dendritic side chains having amide, amine and ester functional groups will allow the accommodation of a number of drug molecules alongwith the synergistic influence of the main chain of the polydendron. On a different front, we have developed[72] novel PAMAM dendritic hydrogel architecture that would be a

promising tool in the field of biomaterials *e.g.* microencapsulation and delivery of drug agents. Further study in this direction is under way in our laboratory.

5 Conclusion

This review has shown the extensive structural developments of a variety of appealing novel synthetic biodegradable polymers that have opened up a new chapter in the field of controlled drug delivery research. We hope this will stimulate polymer chemists, materials scientists, biotechnologists as well as pharmaceutical researchers to develop more innovative and exciting structurally diversed synthetic polymers in the arena of controlled drug delivery.

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