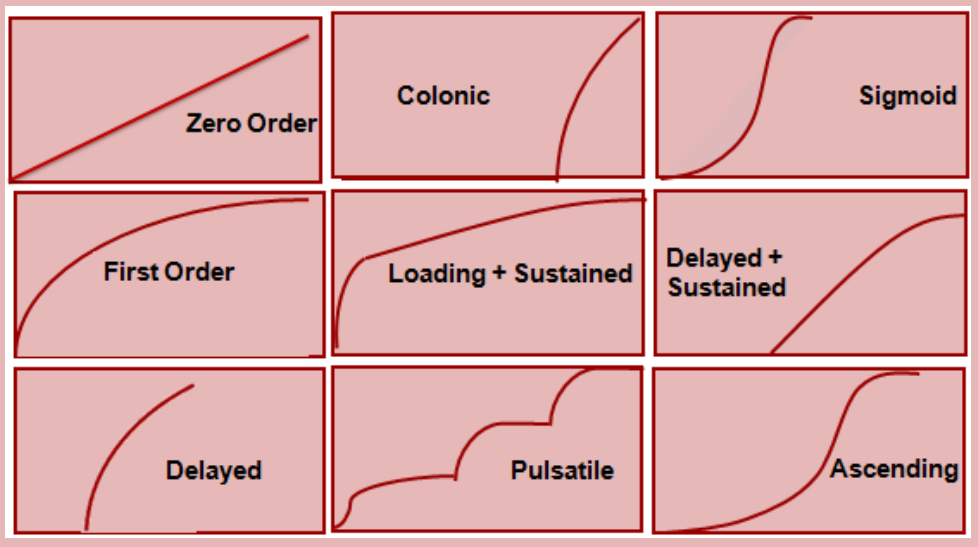
Drug Delivery Systems:

A Review



Editor

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Acknowledgement:

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PREFACE

Men and medicine are inseparable from times immemorial. Although the physical forms of medication have not changed dramatically, the attitude of the public toward accepting medicines have changed with the passage of time.

This fact is also reflected in the strategies adopted by the pharmaceutical companies in the field of research. The cost involved, both in terms of time and money, has made it mandatory for the companies to reconsider their research focus. In an attempt to reduce the cost of drug development process and advantageously reap the benefits of the patent regime, drug delivery systems have become an integral part of the said process.

Drug delivery system is a dosage form, containing an element that exhibits temporal and/or spatial control over the drug release. The ultimate aim of such systems is tailoring of the drug formulation to individual requirements under the control of pathophysiological or in-vivo conditions rather than in-vitro characteristics.

This field of drug delivery systems is dynamic and extensive. Probably it would need an encyclopedia to cover all the types of drug delivery systems. The aim of this book is to compile major drug delivery systems and offer a source of information for all those working in pharmaceutical academia as well as industry.

The book is made available free of charge to all who are interested in the subject for dissemination of knowledge. Authors feel proud to be a part of first of its kind of experiment wherein a technical book is offered for free download through a blog.

We welcome suggestions and criticisms for our readers.

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Table of contents

FUNDAMENTALS OF DRUG DELIVERY SYSTEMS

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Need for Controlled Release Systems:

(Kathryn E. Uhrich 1999)Controlled drug delivery technology represents one of the most rapidly advancing areas of science in which chemists and chemical engineers are contributing to human health care. Such delivery systems offer numerous advantages compared to conventional dosage forms including improved efficacy, reduced toxicity, and improved patient compliance and convenience. Such systems often use synthetic polymers as carriers for the drugs. By so doing, treatments that would not otherwise be possible are now in conventional use. Although the introduction of the first clinical controlled release systems occurred less than 25 years ago, 1997 sales of advanced drug delivery systems in the United States alone were approximately $14 billion dollars. Synthetic polymers used in the controlled release of drugs. Before considering the variety and the evolution of these polymeric structures, it is necessary to examine the motivation for achieving controlled release. This field of pharmaceutical technology has grown and diversified rapidly in recent years. Understanding the derivation of the methods of controlled release and the range of new polymers can be a barrier to involvement from the nonspecialist. All controlled release systems aim to improve the effectiveness of drug therapy. This improvement can take the form of increasing therapeutic activity compared to the intensity of side effects, reducing the number of drug administrations required during treatment, or eliminating the need for specialized drug administration (e.g., repeated injections).

B. Methods of Controlled Release

In temporal control, drug delivery systems aim to deliver the drug over an extended duration or at as specific time during treatment.

Controlled release over an extended duration is highly beneficial for drugs that are rapidly metabolized and eliminated from the body after administration. An example of this benefit is shown schematically in Figure 1 in which the concentration of drug at the site of activity within the body is compared after immediate release from 4 injections administered at 6 hourly intervals and after extended release from a controlled release system. Drug concentrations may fluctuate widely during the 24 h period when the drug is administered via bolus injection, and for only a portion of the treatment period is the drug concentration in the therapeutic window (i.e., the drug concentration that produces beneficial effects without harmful side effects). With the controlled release system, the rate of drug release matches the rate of drug elimination and, therefore, the drug concentration is within the therapeutic window for the vast majority of the 24 h period. Clinically, temporal control can produce a significant improvement in drug therapy. For example, when an opioids pain killer is administered to a patient with terminal cancer, any time that the drug concentration is below therapeutic concentrations the patient experiences pain. A temporally controlled release system would ensure that the maximum possible benefit is derived from the drug. In distribution control, drug delivery systems aim to target the release of the drug to the precise site of activity within the body. The benefit of this type of control is shown schematically in Figure 2 in which

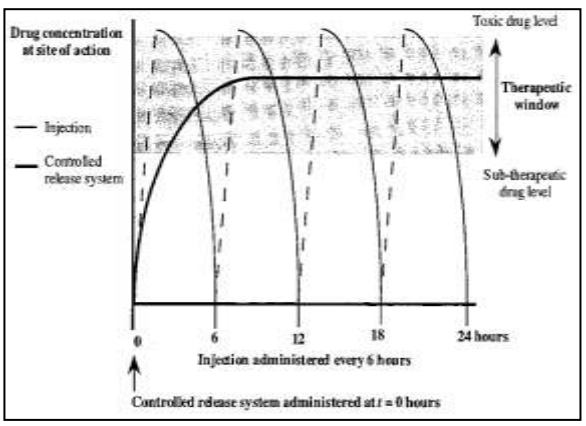

Figure 1. Drug concentrations at site of therapeutic action after delivery as a conventional injection (thin line) and as a temporal controlled release system (bold line). (Kathryn E. Uhrich 1999)

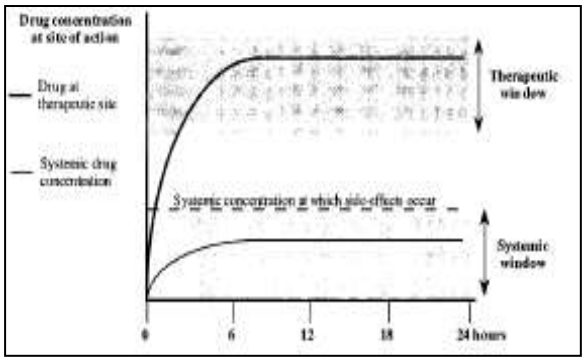

Figure 2. Drug delivery from an ideal distribution controlled release system. Bold line: Drug concentrations at site of therapeutic action. Thin line: Systemic levels at which side effects occur. (Kathryn E. Uhrich 1999)

Drug concentrations at the site of activity and side effect production are compared. There are two principle situations in which distribution control can be beneficial. The first is when the natural distribution causes drug molecules to encounter tissues and cause major side effects that prohibit further treatment. This situation is often the cause of chemotherapy failure when bone marrow cell death prevents the patient from undergoing a complete drug treatment. The second situation is when the natural distribution of the drug does not allow drug molecules to reach their molecular site of action. For example, a drug molecule that acts on a receptor in the brain will not be active if it is distributed by the patient's blood system but cannot cross the blood-brain barrier. A large number of classes of drugs can benefit from temporal or distribution controlled release. These classes include chemotherapeutic drugs, immunosuppressants, anti-inflammatory agents, Antibiotics, opioid antagonists, steroids, hormones, anesthetics, and vaccines. Recently, the need to develop new controlled release strategies has been intensified by advances in the design of peptide drugs and emergence of gene therapy. These biotechnology derived agents may dominate the next generation of drug design. However, their clinical success may be dependent on the design of controlled release devices that ensure that the drugs reach their target cells precisely at the required time. A discussion of the pharmacological and clinical motivations for controlling the release of the specific drug classes referred to above is beyond the limit of this article; however, a number of excellent reviews are available. In addition, it should be noted that controlled release technology is not confined to pharmaceutical applications but has also proven beneficial in agricultural and cosmetic industries. (Kathryn E. Uhrich 1999)

Scope of Polymer Systems:

In this review, a number of polymer backbones that are potentially degradable are detailed in the text. This restriction certainly does not reduce the impact and significance of C-C backbones for controlled release applications but is simply a mechanism to focus on an important subset of materials. To illustrate the diverse range of functionalities available from nonbiodegradable systems based on C-C backbones to heteroatom-containing polymer backbones that may confer biodegradability. (Langer 1998)

Mechanisms of Controlled Drug Release Using Polymers:

A diverse range of mechanisms have been developed to achieve both temporal and distribution controlled release of drugs using polymers. This diversity is a necessary consequence of different drugs imposing various restrictions on the type of delivery system employed. For example, a drug that is to be released over an extended period in a patient's stomach where the pH is acidic and environmental conditions fluctuate widely will require a controlled release system very different from that of a drug that is to be delivered in a pulsatile manner within the blood system. An important consideration in designing polymers for any controlled release mechanism is the fate of the polymer after drug release. Polymers that are naturally excreted from the body are desirable for many controlled release applications. These polymers may be excreted directly via the kidneys or may be biodegraded into smaller molecules that are then excreted. Nondegradable polymers are acceptable in applications in which the delivery system can be recovered after drug release (e.g., removal of patch or insert) or for oral applications in which the polymer passes through the gastrointestinal tract. From a polymer chemistry perspective, it is important to appreciate that different mechanisms of controlled release require polymers with a variety of physicochemical properties. This requirement has stimulated the evolution of the new polymers that will be discussed in section IV. Before consideration of these polymers, the major mechanisms of controlled release and polymeric characteristics that are required to carry out these mechanisms will be briefly. (Kathryn E. Uhrich 1999)

CLASSIFICATION OF DRUG DELIVERY SYSTEM:

Classification of NDDS based on Physical means

1) Osmotic Pressure Activated
2) Hydrodynamic pressure activated
3) Vapor pressure activated
4) Mechanically activated
5) Magnetically activated
6) Sonophoresis
7) Iontophoresis
8) Hydration activated

Classification of NDDS based on Chemical means

1) Hydrolysis activated
2) Ion activated
3) pH activated

Polymers Generally Used for Controlled Drug Delivery System:

1) Poly(esters):

Poly (esters) is the best characterized and most widely studied biodegradable system. The synthesis of poly (esters) has received as much attention as the degradation of these materials. A patent for the use of poly (lactic acid) (PLA) as a resorbable suture material was first filed in 1967.34 The mechanism of degradation in poly (ester) materials is classified as bulk degradation with random hydrolytic scission of the polymer backbone

Polymerization of the cyclic lactone alone is usually too slow to produce high molecular weight material (>20 000 amu). The rate of ring opening for the cyclic lactone can be increased by activation of a Zn- or Snbased catalyst with the carbonyl ester. However, the introduction of a catalyst invites concerns over traces of potentially cytotoxic material. Thus, stannous octoate SnII (CO2CH(*n*Bu)(Et))2 is commonly used because has FDA approval as a food stabilizer.

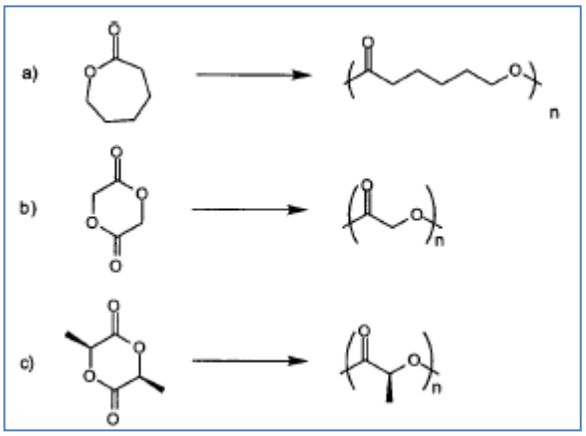

Fig:3 Ring- opening polymerization of selected cyclic lactones to give the following

A) Poly(e-caprolactone)PCL
B) Poly(glycolic acid) PGA
C) Poly(L-lactic acid)PLA (Kathryn E. Uhrich 1999)

1. **Poly(lactic acid), Poly(glycolic acid**), and Their Copolymers Poly(esters) based on poly(lactic acid) (PLA), poly- (glycolic acid) (PGA), and their copolymers, poly(lactic acid-*co*-glycolic acid) (PLGA), are some of the best defined biomaterials with regard to design and performance. Lactic acid contains an asymmetric R-carbon which is typically described as the D or L form in classical stereo chemical terms and sometimes as the *R* and *S* form, respectively. For homopolymers, the enantiomer forms are poly (D-lactic acid) (PDLA) and poly (L-lactic acid) (PLLA). The physicochemical properties of optically active PDLA and PLLA are nearly the same, whereas the racemic PLA has very different characteristics.41 For example, racemic PLA and PLLA have *T*g's of 57 and 56 °C, respectively, but PLLA is highly crystalline with a *T*m of 170 °C and racemic PLA is completely amorphous.

Because the naturally occurring lactic acid is L (or *S*), PLLA is considered more biocompatible. The polymers are derived from monomers that are natural metabolites of the body; thus degradation of these materials yields the corresponding hydroxy acid, making them safe for in vivo use. Biocompatibility of the monomer is the foundation for biocompatibility of degradable polymer systems. To this end, the degradation products often define the biocompatibility of a polymers not necessarily the polymer itself. Even though PLGA is extensively used and represents the gold standard of degradable polymers, increased local acidity due to the degradation can lead to irritation at the site of the polymer

employment. Introduction of basic salts has been investigated as a technique to control the pH in local environment of PLGA implants

From a physical level of understanding, poly (esters) undergo bulk degradation. PLA homopolymers degrade slower than PGA homopolymers on the basis of crystallinity as well as stearic inhibition by the pendent methyl group of PLA to hydrolytic attack. However, the complexity of PLA, PGA, and PLGA degradation has been demonstrated by Vert45 and does not conform to a simple model. Vert and coworkers have demonstrated that size dependence for hydrolytic degradation exists for PLA systems. Other research efforts suggest that PLA-derived micro particles will degrade faster than nanoparticles derived from PLA. This is modeled on diffusion reaction phenomena. An autocatalytic effect at the interior of larger devices is thought to contribute to the initial heterogeneous degradation of larger devices as acidic byproducts cannot readily diffuse out from the interior as is the case for smaller constructs. Extensive degradation studies have also been reported for PLA, poly (caprolactone) (PCL), and their copolymers both in vitro and in vivo.
Studies in hydrolytic degradation for poly (esters) have focused on understanding the effects of changes in polymer chain composition. A distinguishable effect based on end group composition for poly (ester) degradation demonstrated that terminal carboxyl groups have a catalytic effect on hydrolysis for PGA. The ability to tailor rates of protein release from PLGA microspheres was derived from the understanding of end-group effects. The commercial developmental process for formulating poly (esters) with selected drug candidates has been reviewed. The aforementioned review highlights the development of poly (ester) matrices containing human growth hormone that sustained levels of a therapeutic protein in humans for 1 month from a single dose. (Kathryn E. Uhrich 1999)

2. **Poly (ethylene glycol) Block Copolymers:**

Poly (ethylene glycol) (PEG) is also referred to as poly (ethylene oxide) (PEO) at high molecular weights. Biocompatibility is one of the most noted advantages of this material. Typically, PEG with molecular weights of 4000 amu is 98% excreted in man. One of the emerging uses for inclusion of PEG in a controlled release system arises from its protein resistivity. The hydrophilic nature of PEG is such that water hydrogen bonds tightly with the polymer chain and thus excludes, or inhibits, protein adsorption. Many research groups are investigating attachment of PEG chains to therapeutic proteins; PEG chains at the surface allow for longer circulation of the protein in the body by prolonging biological events such as endocytosis, phagocytosis, liver uptake and clearance, and other adsorptive processes.

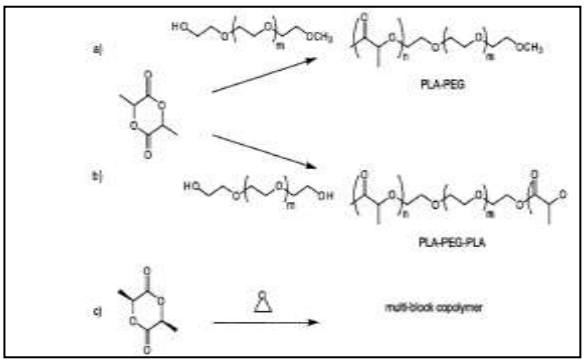

Fig.4 Synthesis of PLA-PEG Copolymer (Kathryn E. Uhrich 1999)

PEG can be made with a range of terminal functionalities which lends to its easy incorporation into copolymer systems. PEG is commonly terminated with chain-end hydroxyl groups which provide a ready handle for synthetic modification. Diblock PLA/ PEG and triblock PLA/PEG/PLA systems have been synthesized and characterized with various PLA contents. The free hydroxyl groups of PEG are ring-opening initiators for lactide in forming the diblock or triblock materials (Figure 5a, b). Recently, Chen et al. have synthesized PLA-PEG multiblock copolymers from L-lactide and ethylene oxide, the monomer precursors for PLA and PEG, respectively (Figure 5c). This approach is different in two respects: (i) use of bimetallic catalysts which proceed by anionic mechanisms; (ii) multiblock polymers are generated. Han and Hubbell further demonstrated the synthetic utility for PLA-PEG systems by introducing acrylate moieties to form cross-linked systems. Similarly, Jeong et al. prepared thermo sensitive PLA-PEO hydrogels that exhibit temperature-dependent gel-sol transition for use as injectable drug delivery systems.

Poly (ortho esters):

The motivation for designing poly (ortho esters) for drug delivery was the need to develop biodegradable polymers that inhibited drug release

by diffusion mechanisms and allowed drug release only after the hydrolysis of polymer chains at the surface of the device.70 Most research on poly (ortho esters) has focused on the synthesis of polymers by the addition of polyols to diketene acetals. For example, Heller et al. have described the synthesis and application of the 3, 9-diethylidene-2, 4, 8, 10-tetraoxaspiro [5.5] undecane (DETOSU)-based poly (ortho esters).71 The basic structure is formed by the addition of the DETOSUmonomer to a diol to form the chemical structure. The DETOSU-based poly (ortho esters) contain acid labile ortho ester linkages in their backbone structure. Within aqueous environments, the ortho ester groups are hydrolyzed to form Pentaerythritol dipropionate and diol monomers as breakdown products. The Pentaerythritol dipropionate is further hydrolyzed to Pentaerythritol and acetic acid. Acid-catalyzed hydrolysis of these polymers can be controlled by introducing acidic or basic Excipients into matrixes. Rates of hydrolysis can be increased by the addition of acidic excipients, such as suberic acid, as demonstrated by the zero-order release of 5-fluorouracil over a 15 day period.72 Alternatively, basic excipients stabilize the bulk of the matrix but diffuse out of the surface region, thereby facilitating surface-only erosion. This approach has been employed in the temporal controlled release of tetracycline over a period of weeks in the treatment of periodontal disease.

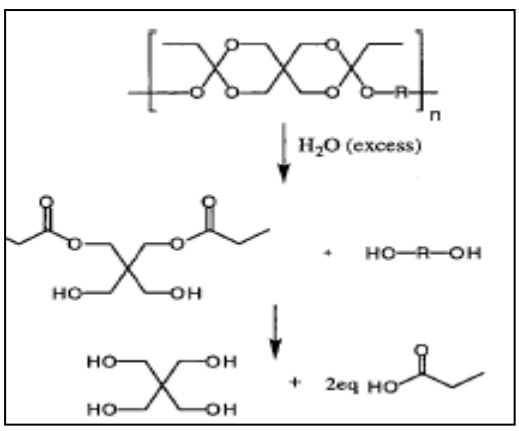

Fig.5: Degradation of 3, 9(bis ethylidene-2, 4,8,10 Tetraoxaspiro undecane (DETOSU) based poly ortho ester (Kathryn E. Uhrich 1999)

A useful feature of the DETOSU systems is the ability to control the mechanical properties by changing the diol monomer ratios within the final polymeric structure. For example, Heller et al. have shown that the glass transition temperature of polymers containing a rigid diol monomer (*trans*cyclohexanedimethanol) and a flexible monomer (1, 6- hexanediol) could be varied between 20 and 105° by increasing the proportion of the rigid diol. This control can also be achieved with the glycolide containing polymers.

A number of applications have been described for cross-linked poly (ortho esters) formed by the substitution of 1, 2, 6-hexanetriol for 1, 2-hexanediol, for example. The triol monomer allows cross-linked materials to be formed that are semisolid materials. It has been envisaged that these materials could be injected into the patient as a viscous liquid at slightly elevated temperatures that form nondeformable depot implants upon cooling. (V. Balmurlidhara 2011)

Poly (anhydrides)

To obtain a device that erodes heterogeneously, the polymer should be hydrophobic yet contain water sensitive linkages. One type of polymer system that meets this requirement is the poly (anhydrides). Poly-(anhydrides) undergoes hydrolytic bond cleavage to form water-soluble degradation products that can dissolve in an aqueous environment, thus resulting in polymer erosion. Poly (anhydrides) are believed to undergo predominantly surface erosion due to the high water liability of the anhydride bonds on the surface and the hydrophobicity which prevents water penetration into the bulk. This process is similar to the slow disappearance of a bar of soap over time. The decrease in the device thickness throughout the erosion process, maintenance of the structural integrity, and the nearly zero-order degradation kinetics suggest that heterogeneous surface erosion predominates. The majority of poly (anhydrides) are prepared by melt-condensation polymerization. Starting with a dicarboxylic acid monomer, a prepolymer of a mixed anhydride is formed with acetic anhydride. The final polymer is obtained by heating the prepolymer under vacuum to remove the acetic anhydride byproduct. The most widely studied poly (anhydrides) are based on sebacic acid (SA), *p*-(carboxyphenoxy) propane (CPP), and *p*-(carboxyphenoxy) hexane (CPH)

Degradation rates of these polymers can be controlled by variations in polymer composition. The more hydrophobic the monomer, the more stable the anhydride bond is to hydrolysis. Aliphatic poly- (anhydrides) (e.g., SA) degrade within days whereas aromatic poly (anhydrides) (e.g., CPH) degrade over several years.

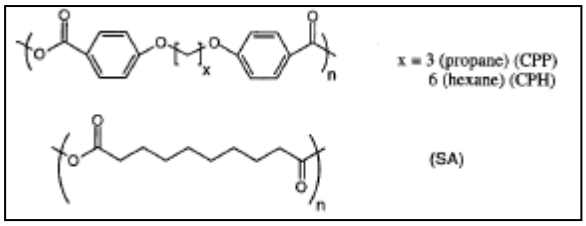

Fig: 6 Structure of widely used aromatic poly (anhydrides) based on monomer of p-carboxy phenoxy propane (Kathryn E. Uhrich 1999)

The biocompatibility of copolymers of SA and CPP has been well established. Evaluation of the toxicity of poly (anhydrides) show that they possess excellent in vivo biocompatibility.81 Recent clinical trials have demonstrated that an intracranial device of SA/CPP copolymers improves the therapeutic efficacy of an antitumor agent, bischloronitrosourea, for patients suffering from a lethal type of brain cancer.

Poly (anhydride-esters)

Other modifications of poly (anhydrides) include poly (anhydride-esters), which include two different types of hydrolytically cleavable bonds in the polymer backbone. In one example, low molecular weight carboxylic acid-terminated prepolymer of poly (_- caprolactone) were coupled via anhydride linkages. The intent of this research was to design polymers that displayed two-stage degradation profiles: anhydride bonds rapidly hydrolyzed to the poly (ester) prepolymer which degraded much more slowly. In another example, carboxylic acid-terminated monomers that contain ester bonds are activated and then polymerized using the same chemistry described for the poly (anhydrides). A unique aspect of these poly (anhydride-esters) is that hydrolytic degradation of the polymer backbone yields a therapeutically useful compound, salicylic acid. Polymer's degradation products are potentially beneficial

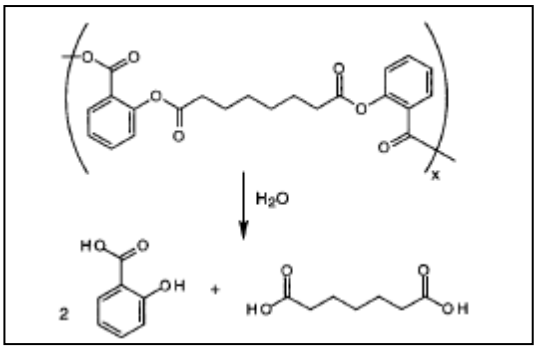

Fig: 7 Poly (anhydride ester that undergo into salicylic acid, an anti inflammatory agent (Kathryn E. Uhrich 1999)

Poly (amides):

The most interesting class of poly (amides) for controlled release are the poly (amino acids). The synthetic ability to manipulate amino acid sequences has seen its maturity over the last two decades with new techniques and strategies continually being introduced. An excellent review of the histo4ry of amino acid-derived polymers is given by Nathan and Kohn.93 Poly(amino acids) have been used predominantly to deliver low molecular weight drugs, are usually tolerated when implanted in animals,94 and are metabolized to relatively nontoxic products. These results suggest good biocompatibility, but their mildly antigenic nature makes their widespread use uncertain. Another concern with poly (amino acids) is the intrinsic hydrolytic stability of the amide bond which must rely upon enzymes for bond cleavage. The dependence on enzymes generally results in poor controlled release in vivo. The expense and difficulty in production of elaborate polypeptide sequences has limited the composition to homopolymers, predominantly poly (glutamic acid) and poly (aspartic acid). Poly(amino acids) are generally hydrophilic with degradation rates dependent upon hydrophilicity of the amino acids.96,97 Amino acids are attractive due to the functionality they can provide a polymer. For example, poly (lactic acid-*co* lysine) (PLAL) was synthesized using a stannous octoate catalyst from lactide and a lysine-containing monomer analogous to lactide. Inclusion of the amino acid lysine provides an amino group that allows for further modification of the PLAL system. Recently, peptide sequences that promote cell adhesion have been attached to PLAL.

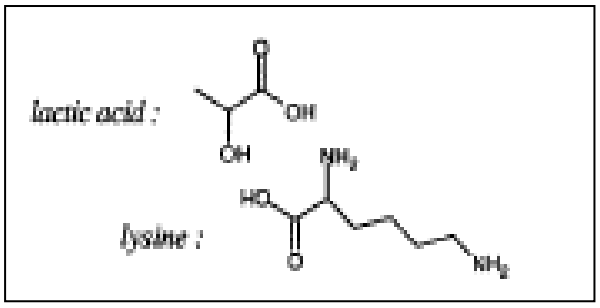

Fig.8 Poly (lactic acid-co-amino acid) PLAL Polymer system (Kathryn E. Uhrich 1999)

Currently marketed oral controlled-release systems:

Advances in oral controlled-release technology are attributed to the development of novel biocompatible polymers and machineries that allow preparation of novel design dosage forms in a reproducible manner. The main oral drug-delivery approaches that have survived through the ages are as follows:

- Coating technology using various polymers for coating tablets, nonpareil sugar beads, and granules
- Matrix systems made of swell able or nonswellable polymers
- Slowly eroding devices
- Osmotically controlled devices.

Conventional tablet formulations are still popular in the design of single-unit, matrix-type controlled release dosage forms. The advancement of granulation technology and the array of polymers available with various physicochemical properties (such as modified cellulose or starch derivatives) have made the development of novel oral controlled release systems possible. Matrix devices made with cellulose or acrylic acid derivatives, which release the homogeneously dispersed drug based on the penetration of water through the matrix, have gained steady popularity because of their simplicity in design. The drawback of matrix-type delivery systems is their first-order drug delivery mechanism caused by changing surface area and drug diffusional path length with time. This drawback has been addressed by osmotic delivery systems, which maintain a zero-order drug release irrespective of the pH and hydrodynamics of the GI tract. Multiparticulate systems are gaining favor over single-unit dosage forms because of their desirable distribution characteristics, reproducible transit time, and reduced chance of gastric irritation owing to the localization of drug delivery.

Although several technologies for the production of microparticulate systems have been designed, thus far the mainstream technologies are still based on spray-drying, spheronization, and film-coating technology.

FDA regulation of oral Controlled-release drugs:

In the 1980s, FDA introduced rigorous regulations governing bioequivalence and in vitro–in vivo correlations for controlled-release products. Required pharmacokinetic evaluations involve

- relative bioavailability following single dose
- relative bioavailability following multiple doses
- effect of food
- dose proportionality
- unit dosage strength proportionality
- single-dose bioequivalence study

(Experimental versus marketed formulations at various strengths)

- In vivo–in vitro correlation
- Pharmacokinetic/pharmacodynamic (PK/PD) relationship.

In general, for drugs in which the exposure–response relationship has not been established or is unknown, applications for changing the formulation from immediate release to controlled release requires demonstration of the safety and efficacy of the product in the target patient population. When an NME is developed as a controlled-release dosage form, additional studies to characterize its absorption, distribution, metabolism, and excretion (ADME) characteristics are recommended.

The future of Drug Delivery System:

The future of controlled-release products is promising, especially in the following areas that present high promise and acceptability:

- Particulate systems: The micro particle and nanoparticle approach that involves biodegradable polymers and is aimed at the uptake of intact drug-loaded particles via the Peyer's patches in the small intestine could be useful for delivery of peptide drugs that cannot, in general, be given orally.
- Chronopharmacokinetic systems: Oral controlled drug delivery with a pulsatile release regimen could effectively deliver drugs where need exists to counter naturally occurring processes such as bacterial/parasitical growth patterns (e.g., the once-daily oral Pulsys system introduced by Advancis Pharmaceutical Corp., which could potentially inhibit the emergence of resistant strains of microorganisms).
- Targeted drug delivery: Oral controlled drug delivery that targets regions in the GI tract and