Chapter 5

Lactic acid co-polymers: Synthesis and application in sustained drug release
5.1 Introduction:

For the last 60 years, synthetic polymeric materials have become one of the most attractive domains in materials science. This success is primarily due to their low cost, their reproducibility, and their resistance to physical aging and biological attacks. However, the resistance of synthetic polymers to the degrading action of living systems is becoming more and more problematic in several applications where they are used for a limited period of time before becoming wastes. It is the case in surgery, in pharmacology, in agriculture, and in the environment as well. In such applications, degradation resistant polymeric wastes are less and less acceptable (Vert, 2005).

Basically, any artificial polymeric device or macromolecule that is to be used as material in contact with a living system for a limited period of time only, should be eliminated and ideally biorecycled after use to avoid storage as a waste. This is true in the case of the animal and human bodies where high-molecular-weight polymeric compounds are entrapped between skin and mucosa and cannot cross cell-made parenteral physiological membranes such as the blood-brain barrier or the vascular walls (Vert, 2005).

To achieve biorecycling, mother nature had to find processes to recycle proteins or polysaccharide-type biopolymers. Indeed enzymatic degradation is outstandingly efficient, selective, and appropriate to ensure the turnover in living systems. However, in the world of degradable polymers, one must consider that enzymes can be present in nature only if living cells are present, and that bioactive enzymes can be present only if the right cells are present. These requisites are sometimes ignored in the search for natural or artificial polymers and polymeric matters that could serve as biodegradable material and be eliminated and recycled via natural pathways when they become waste. The fact that poly(glycolic acid) does not require an enzyme to be degraded in the human body was one of the reasons for it to become the first artificial, degradable polymer to be developed as suturing material in the early 1960s. Aliphatic polyesters, especially those that can generate hydroxyl acid monomers as metabolites during degradation like poly (β- hydroxy butyrate), PHB, poly(β-malic acid), PMLA, poly- (ε-caprolactone), PCL, or poly (R-hydroxy acids
5.2 Biomedical field and corresponding applications:

Figure 5.1 shows the schematic representation of some of the therapeutic devices relevant to the concept of elimination after use that are clinically used or are presently at the level of scientific investigation in human or animal.

- **Implant**

- **Injectables**
  - Microparticles (> 1000 nm)
  - Nanoparticles (<1000 nm)
  - Self assemblies
    - Micelles (~ 50-150 nm)
    - Aggregates (~ 50-200 nm)
    - Monomolecular globule (~ 5-8 nm)
  - Polyelectrolyte complexes
  - Macromolecular prodrugs

- **Hydrogels**

Figure: 5.1 Schematic representation of the various therapeutic systems that are relevant to the use of bioresorbable/biodegradable polymeric items in temporary therapy based on the outstanding self-healing capacity of living systems here.

Regarding pharmacology and polymer-based controlled drug delivery, the advantages expected from therapeutic devices are multiple: protect the bioactive drug from the aggression of the host, protect the host from the toxicity of the drug, increase the therapeutic index (or drug efficiency for a given dose), avoid repeated administrations, increase the solubility of hydrophobic drug molecules in water, deliver the drug at predetermined doses and rates, target some cells or organs, and so forth. The number of devices or systems that are presently under investigation in pharmacology is large (Fig. 5.1). These are smart systems regarded as promising to deliver large molecules such as proteins or even large hydrophilic molecules and lipophilic small molecules at the same time. Because they are to be used for a limited period of time, all these systems require degradable polymers to fulfill the criterion of
elimination after use. They also have to fulfill many other requirements related to the
the human body and specific regulations (Vert, 2005).

5.3 Aliphatic polyesters:

Aliphatic polyesters are members of a large family of polymers that are either
from natural origin [bacterial poly- (β-hydroxy acid)s, β-PHA] or from chemical
origin (polycondensation of hydroxy acids and of diacids and dialcohols or
polymerization of lactone-type heterocycles) (Doi and Steinbuchel, 2002; Albertsson,
2002; Li and Vert, 2002)

5.3.1 Chemically Derived Aliphatic Polyesters:

Aliphatic polyesters synthesized either by polycondensation of hydroxyl acids
or diacids and diols, or by polymerization of lactone type heterocycles are not
biopolymers (Albertsson, 2002). Indeed, they are not found as such in living systems.
The confusion comes from an improper use of the word biodegradable that must be
reserved for cell-mediated degradation and not applied to abiotic enzymatic
degradation. The fact that a synthetic polymer can be enzymatically attacked under
laboratory conditions does not imply that the same polymer is going to be
biodegradable in the nature. The presence of the right cells and life-permitting
conditions are mandatory. From this viewpoint, poly e-caprolactone (PCL), poly β-
hydroxyalkanoates (PHAs), are biodegradable in the environment whereas their
degradation in human is based on hydrolysis (Djamaraju et al, 2003; Barbault et al,
2002).

Basically, the degradation of polymers via non enzymatic chemical routes is
easier to control by chemists. However, the special features of hydrolytic degradation
of aliphatic polyester-based matrixes are a source of complications that make the
degradation control difficult. For many years, their degradation in aqueous media, that
is, *in vitro* as well as *in vivo*, was regarded as homogeneous, although surface erosion
was claimed in a few cases. When such a device made of a lactic acid-based polymer
is placed in contact with an aqueous medium, water penetrates into the specimen and
the hydrolytic cleavage of ester bonds starts as well as autocatalysis. Water absorption
is, thus, a critical factor. For a time, the partially degraded macromolecules remain
insoluble in the surrounding aqueous medium and the degradation proceeds homogeneously. However, as soon as the molecular weight of some of the partially degraded macromolecules becomes low enough to allow dissolution of the formed oligomers in the surrounding aqueous medium, the diffusion of these oligomers starts within the whole bulk, with the soluble compounds moving slowly to and off the surface while they continue to degrade. This process, that combines diffusion, chemical reaction, and dissolution phenomena, results in differentiation between the rates of degradation at the surface and interior of the matrix (Li et al, 1990 a, b). In vivo, where the medium is buffered, neutralization of terminal carboxyl groups might also contribute to discriminate the surface degradation rate.

Basically, there are four main factors which condition the diffusion-reaction-dissolution phenomena: (i) the hydrolysis rate constant of the ester bond (ii) the diffusion coefficient of water within the matrix (iii) the diffusion coefficient of chain fragments within the polymeric matrix and (iv) the solubility of degradation products, generally oligomers, within the surrounding liquid medium from which penetrating water is issued (Vert et al, 1997).

Bioresorbable (degradable with proved elimination from the human body), and biorecyclable (in the environment) lactic acid based devices and products are presently at the commercial stages including matrixes to make surgical devices (sutures, bone plates, and screws and filling material for bone reconstruction or plastic surgery), controlled drug delivery systems in pharmacology and packaging materials (Gruber and O'Brien, 2002; Kawashima et al, 2002). Indeed, below $T_g$ (glass transition temperature, the temperature at which polymer looks like a glass), these polymers are rigid and exhibit rather good mechanical properties that can be compared with those of commodity polymers. However, they cannot provide alternatives to functional polymers satisfactorily, because of the absence of functional groups to enlarge the range of properties and to generate properties such as hydrophilicity, chemical reactivity, and even smartness that are available in the families of biostable polymers and are necessary for some of the applications mentioned in table 5.1 and figure 5.1. There are many applications of aliphatic polyesters, especially those derived from lactic acid as shown in table 5.1 and they must fulfill certain criteria. First, the polymeric backbone has to be biocompatible,
degradable, or biodegradable and able to generate degradation by-products that are also biocompatible and that can be eliminated or bioassimilated (animal and human body) or bioassimilated and biorecycled (environment). Second, the polymer must be able to generate devices with properties analogous to those of the biostable material to be replaced. Last but not the least, degradation characteristics have to be in harmony with the functional characteristics and conditions imposed by the living system. Aliphatic polyesters, especially lactic acid-based polymeric systems, have a potential to provide bioresorbable and biorecyclable matrixes and devices of practical interest (Vert, 2005).

<table>
<thead>
<tr>
<th>Biomedical</th>
<th>Environment</th>
</tr>
</thead>
<tbody>
<tr>
<td>Surgery</td>
<td>Packaging</td>
</tr>
<tr>
<td>Sutures</td>
<td>Washing products</td>
</tr>
<tr>
<td>Osteosynthesis devices</td>
<td>Cartridge for gun</td>
</tr>
<tr>
<td>Tissue engineering</td>
<td>Cartridge wad</td>
</tr>
<tr>
<td>Wound dressing</td>
<td>Cigarette filters</td>
</tr>
<tr>
<td>Pharmacology</td>
<td>Agriculture</td>
</tr>
<tr>
<td>Controls drug delivery</td>
<td>Sustained delivery of pesticides, insecticides, pheromons and fertilizers</td>
</tr>
<tr>
<td>Bioactive macromolecules</td>
<td>Seed protection</td>
</tr>
<tr>
<td>Packaging</td>
<td>Mulching films</td>
</tr>
</tbody>
</table>

Table: 5.1 Main applications of polymers relevant to resorbable and biorecyclable polymers and comparison between the biomedical and the environmental fields

Controlled release systems have evolved out of a continuing need for prolong and better control drug administration. Sustained drug release was first attempted in around 1930s, by combining drugs with substances that decreased their solubility, by compressing them into dense tablets, and coating them with materials that did not dissolve readily in gastric juices. These methods enabled the drug to be effective for longer periods but the problem of over dosing and lower dosing was associated with such systems. Sustained release systems were first developed in the 1950s and were used to administer non-medical agents like pesticides and anti-fouling substances. These types of systems were first used in medicinal research in 1960s, and in the 1970s, systems were developed for the slow release of large weight molecules like polypeptides (Brook and Van 1984; Hoes and Feigen, 1989; Langer, 1989; Langer, 1990; Langer et al 1990).
The science of sustained release has been regarded as a separate technology. The discovery and development of novel pharmaceuticals in the past fifty years have resulted in the improved treatment of human and animal diseases. The parallel progress in designing new strategies in the delivery of such carriers to the desired site of action avoided loss of drug activity and prevented toxicity. Importantly, these systems must be cost-effective and convenient to the patient. The development of Novel Drug Delivery Systems (NDDS) has fulfilled this requirement. Such NDDS promise the rendering of drugs safer, more effective, less toxic, and thus more cost-effective. There is a strong impetus to create rapid and successful drug delivery systems recently (Kim and Peppas, 2002; Kanikanti et al, 2002, Loo-Teck, et al, 2002).

Controlled release systems can be distinguished from conventional pharmaceutical dosage forms as they can alter drug absorption by modifying the release rate. This may lead to reduced fluctuations in the plasma drug concentration, increased apparent half-life and sustained drug effects. Assuming certain absorption and metabolism characteristics, a constant release rate may result in constant blood levels of the drug and maximize the duration for which drug levels are in the therapeutic range. The ideal drug delivery systems should be inert, biocompatible, mechanically strong, comfortable for the patient, capable of high drug loading, prevent accidental release of biologically active compound (BAC), easy to administer and remove, and simple to fabricate and sterilize.

The goal of many original controlled release systems was to achieve high level of drug in blood over a longer period. For conventional drug delivery modes such as spray, an injection, or the taking of pill, drug concentration in the blood raises, peaks, and then declines till the next administration of dosage (Fig. 5.2). Since each drug is toxic above and ineffective below a particular concentration the plasma drug concentration in any patient at a particular time depends on compliance with prescribed routine. This is particularly problematic if the toxic and effective levels are closer. The goal of a controlled release system is to maintain the drug concentration between these two levels for a prolonged time using a single dosage form (Fig. 5.3). Depending on the formulation and application, the duration of drug delivery may vary from 24 h, to months and to years.
5.4 Advantages of sustained drug release systems:

Sustained drug delivery systems have several advantages (Samour, 1978; Gardner, 1985; Langer et al, 1990).

1. Drug/ BAC (biologically active compound) can be delivered to the target organs in the desired amount at a particular time, either by combination of active compound with polymer or by placing the BAC in a polymeric delivery system systematically with ease.

2. Several drugs can be actively coupled with the same polymeric matrix.

3. Alteration and modification activity of the drug can be performed by systematic changes in solubility and rate of diffusion.

4. Dosage frequency can be minimized.

5. Toxicity of the drug can be lowered depending on the drug and the polymeric material used.
6. Fluctuation in blood level of the drug can reduced.
7. Side effects like nausea, gastric irritation, etc. can be minimized.
8. Uniform response can be achieved through these systems.
9. Cost-effective treatment can be possible due to minimization in dosing frequency.
10. Patient's compliance and convenience can be increased.

5.5 Disadvantages of sustained-release drug delivery systems:

1. The effect of polymer matrix on the biological environment of the body during administration.
2. Catastrophic failure (dose dumping) of a formulation could occur due to release of BAC, four to six times of the usual dose, may cause severe side effects and increase toxicity, particularly if a drug has a narrow therapeutic index.
3. Technology is much more expensive in comparison with the conventional dosage forms.

5.6 Technologies for sustained drug release systems:

5.6.1 Physical entrapment:

Entrapment of a BAC in a matrix without any chemical bonding was first investigated by Langer et al (1990). A large number of carriers differing in their physicochemical properties and hence loading characteristics are available, like polyvinyl pyrrolidone copolymeric hydrogels, hydrogels of natural modified polymeric matrices (Kawashima and Murata, 2001; Franke and Schering, 2004), polymeric micro spheres of natural and synthetic origin and also natural carriers like cells (erythrocytes), and lipoproteins (Dawson et al, 1987; Mallabone et al, 1988).

5.6.2 Liposomes:

They can be readily directed to biomembranes. Liposomes are spherical lipid bilayers ranging from 50 nm to 1000 nm in diameter. They serve as convenient delivery vehicles for biologically active molecules. The most common method of preparing liposomes is the ultra sonication of lipid suspension in water. They can also
be prepared by the dialysis of surfactant lipid mixture and with shaking of lipid films on glass surfaces with water. A number of possible applications in therapeutic and preventive medicine by the transport of drugs through liposomes to phagocytic cells have been reported. Intracellular transport of drugs for removal of unwanted materials is also facilitated by liposomes. Several research laboratories have shown liposomes to act as powerful immunological adjuvant to include both humoral and cellular immunity for a variety of bacterial and viral antigens relevant to diseases like diphtheria, hepatitis B, cholera and influenza (Gregoriadis, 1981).

5.6.3 Micro encapsulation:

A solid particle or a liquid droplet is coated with a polymer in the process of micro encapsulation. Micro encapsulation can be either biocompatible or biodegradable depending on the polymer matrix.

Biodegradable polymers used for this purpose, include poly (α - hydroxy acid), poly (DL - lactic acid), poly (DL - lactic - co-glycolic acid), and natural polymers like cross linked albumin. Micro encapsulations for oral drug delivery systems are employed to sustain release of the drug and reduce or to eliminate gastrointestinal tract irritation (Patel JV, 2005). Nanoparticles or nanocapsules are similar to micro encapsulation in principle.

5.6.4 Micro emulsions:

Micro emulsions were first obtained by preparing a normal emulsion of soap, water and a hydrocarbon, and adding a medium chain alcohol like pentanol to that emulsion. The nature and structure of the surfactant, co-surfactant and oil are essential factors in formulating microemulsions. Microemulsions show higher rate of diffusion compared to gels and for other studies (Sengupta and Papadopoulos, 1992).

In the present study, aliphatic polyesters of lactic acid were made with other hydroxy acids and alcohols like citric acid, glycerol and penta erythreitol. These polyesters were studied for their ability for sustained release of a model drug \textit{in vitro}. 
5.7 Materials and Methods:

5.7.1 Materials:

Lactic acid (99 %) was purchased from Hi-Media, Mumbai, India. Citric acid and glycerol were purchased from Rankem, Maharashtra, India and E-Merk (India) Ltd. Mumbai, India and used as received. Toluene used as received from E-Merk (India) Ltd.

5.7.2 Preparation of co-polymers:

Lactic acid, citric acid and glycerol were charged into 250 ml round bottom flask in the molar ratio of 1:1:1. The flask was heated upto 200 °C in an oil bath and during progress of reaction the by-product water was continuously removed azeotropically with toluene. After the completion of reaction time, the traces of water trapped in co-polymer were removed under reduced pressure. White solid crystalline product was obtained and stored in a vacuum desiccator. Other co-polymers were prepared by varying the molar ratio of glycerol to 1:1:1.1 and 1:1:1.2. Penta erythritol was also used in same manner instead of glycerol.

5.7.3 Drug incorporation:

Dry polymer was immersed in a solution of diclophenac sodium (10 % w/w of polymer) in methanol for 12 h. After equilibrium swelling, the swollen polymer was removed and dried in vacuo leaving the drug uniformly distributed throughout the polymer. The amount of the drug entrapped was determined spectrophotometrically (Helios-α, Thermospectronic, NY, USA) from the solution at the $\lambda_{\text{max}}$ of the drug (283 nm) in methanol.

5.7.4 In vitro drug release:

Release of the drug from the co-polymer under physiological conditions was studied by placing the drug loaded polymer in 20 ml of phosphate buffer pH 7.4 at 30 °C under unstirred condition. At different time intervals all the buffer was removed and 20 ml of fresh buffer was added. Released drug (diclophenac sodium) was estimated spectrophotometrically after appropriated dilution and filtration through whatmann filter paper No.1. Concentration of the drug was then computed by
comparison with the standard curve prepared in the same buffer within the appropriate concentration range. The blot dried polymer was weighed on electronic balance (Dhona 100DS, D=0.01mg) in between the buffer change.

5.7.5 Swelling kinetics:

To correlate the swelling tendency of these copolymers with their drug-releasing capacity, the swelling behavior of the drug-loaded gels was studied. The degree of swelling at different time intervals was calculated by the following expression (equation-1).

\[
\text{Degree of swelling} = \frac{W_t - W_0}{W_0} \times 100\% 
\]

Where the amount of water sorbed, \(W_o\), is reported as a function of time and the equilibrium sorption at an infinity long time is designated as \(W_0\). \(n\) is the swelling exponent, which is denoted by the following equation-2.

\[
\frac{Q_t}{Q_0} = \kappa \times t^n
\]

Where, \(Q_t\) and \(Q_0\) are the mass uptake of the solvent at time \(t\) and at equilibrium, respectively. \(\kappa\) is a characteristic constant of the polymer and \(n\) is the characteristic exponent of the mode transport of the penetrate. On taking the natural log of equation-2,

\[
\ln\left(\frac{Q_t}{Q_0}\right) = \ln\kappa + \ln t
\]

Values of \(n\) and \(\kappa\) were calculated from the slope and the intercept of the plot of \(\ln Q_t/Q_0\) against \(\ln t\), respectively.

5.7.6 Characterization of copolymers:

Copolymers were characterized by differential scanning calorimetry (DSC), thermal gravimetric analysis (TGA) and fourier transformation infrared (FTIR) spectroscopy.
5.7.7 Molecular weight between two crosslinks by swelling study:

Average molecular weight between two crosslink points ($M_c$), which is a direct measure of crosslinking density, was determined by the well-known Flory Rehner equation-4 (Flory and Rehner, 1943; Flory, 1950; Flory, 1953).

$$M_c = \frac{-\rho V_1 (V_p)^{\frac{1}{p}}}{\ln(1-V_p) + V_p + \chi_{12} V_p^2}$$  \hspace{1cm} (4)

Where $M_c$ = Molecular weight between two crosslinks, $V_1$ = molar volume of solvent, $\rho$ = density of network, $V_p$ = volume fraction of polymer in swollen state which is calculated by following equation-5.

$$V_p = \frac{\frac{W_p}{d_p}}{\frac{W_p}{d_p} + \frac{W_s}{d_s}}$$ \hspace{1cm} (5)

Where $W_p$ = weight of dry polymer, $d_p$ = density of polymer, $W_s$ = weight of solvent taken up at equilibrium, $d_s$ = density of solvent, $\chi_{12}$ = polymer-solvent interaction parameter which was calculated by the following equation-12 (Eagland et al, 1994).

$$\chi_{12} = B + \frac{V_1 (\delta_p - \delta_s)^2}{RT}$$ \hspace{1cm} (6)

Where $\delta_p$ = solubility of polymer, $\delta_s$ = solubility parameter of solvent, $R$ = gas constant, $T$ = absolute temperature, $B$ = Lattice constant which is generally taken as 0.34 for good solvent, all the other terms in equation-12 are negligible for good solvent.
5.8 Results and Discussion:

5.8.1 Effect of molar ratio on polymer:

Molar ratio is the term related to the reciprocal amount of one functional group of one monomer to the other functional group of another monomer. Molar ratio of either monomer or the functional group is the most important when polymer properties are to be manipulated.

In present study, monomers possessing –OH and –COOH functional groups were selected, namely lactic acid, citric acid and glycerol / pentaerythritol. Thus co-polymers produced would have one –OH and one –COOH from lactic acid, three –COOH and one –OH from citric acid and either three –OH from glycerol or four –OH groups from pentaerythritol.

Lactic acid

\[
\text{HO—C—H} \\
\text{CH}_3
\]

Citric acid

\[
\text{HO—C—COOH} \\
\text{COOH}
\]

Glycerol

\[
\text{H}_2\text{C—OH} \\
\text{H—C—OH} \\
\text{H}_2\text{C—OH}
\]

Pentaerythritol

\[
\text{HO} \\
\text{OH}
\]

\[
\text{HO} \\
\text{OH}
\]

Co-polymers were white solid mass and were mechanically stable at ambient temperature and can be handled with ease. The ultimate products of the hydrolytic degradation of the co-polymers are expected to be lactic acid, citric acid and either glycerol or pentaerythritol. Lactic acid, citric acid and glycerol are biologically acceptable and pentaerythritol is used as a blood anticoagulant medicine. These co-polymers have been used for drug entrapment to investigate its efficacy for in vitro drug release.
5.8.2 Drug release:

Model drug used in the present study was the diclofenac sodium. It is a non-steroidal anti inflammmatory drug (NSAID) advocated for use in painful and inflammatory rheumatic and certain non rheumatic conditions. It is available in number of administration forms which can be given orally, rectally and intra muscularly. In number of trials, its efficacy has been equivalent to that of many newer and established NSAIDs, with which it has been compared. As an analgesic it has a fast onset and long duration of action. It is well tolerated, compared with other NSAIDs, and rarely produces gastrointestinal ulceration or other serious side effects. Thus it can be considered as one of the few NSAIDs of ‘first choice’ in the treatment of acute and chronic painful and inflammatory conditions. (ADIS Drug Information Services, Auckland).

![Calibration curves of sodium diclofenac](image)

**Figure: 5.4 Calibration curves of sodium diclofenac; a, phosphate buffer; b, methanol**

Diclofenac sodium

The effect of molar ratio of monomer on total drug release from co-polymers was investigated. The copolymers prepared in different molar ratio are designated as follows:
Table: 5.2 Composition of the co-polymers

<table>
<thead>
<tr>
<th>Code</th>
<th>Lactic acid (mol)</th>
<th>Citric acid (mol)</th>
<th>Glycerol (mol)</th>
<th>Pentaerythritol (mol)</th>
</tr>
</thead>
<tbody>
<tr>
<td>G1</td>
<td>1</td>
<td>1</td>
<td>1.0</td>
<td>0</td>
</tr>
<tr>
<td>G2</td>
<td>1</td>
<td>1</td>
<td>1.1</td>
<td>0</td>
</tr>
<tr>
<td>G3</td>
<td>1</td>
<td>1</td>
<td>1.2</td>
<td>0</td>
</tr>
<tr>
<td>P1</td>
<td>1</td>
<td>1</td>
<td>0</td>
<td>1.0</td>
</tr>
<tr>
<td>P2</td>
<td>1</td>
<td>1</td>
<td>0</td>
<td>1.1</td>
</tr>
<tr>
<td>P3</td>
<td>1</td>
<td>1</td>
<td>0</td>
<td>1.2</td>
</tr>
</tbody>
</table>

Drug loading capacity of co-polymers decreased with increase in the molar ratio of both glycerol and pentaerythritol. Drug loading up to 9.92%, 7.8% and 7.2% was obtained with G1, G2 and G3 co-polymers whereas 10%, 6.96% and 4.88% drug loading was obtained with P1, P2 and P3, respectively.

Drug release pattern was similar for all type of co-polymers. Among the polymers final achievable released drug concentration was different and decreased in accordance with molar ratio and thereby drug loading. Drug release pattern was characterized by the initial burst phase where in rapid drug release was obtained followed by slow and steady release over a period of time. (Fig. 5.5a and b). This is due to the phenomenon in which the outer surface comes in immediate contact with the buffer solution, which results into fast diffusion of solvent and followed by drug release. Similar observations were also made by the other workers.

Using glycerol, drug release could be sustained up to five days whereas this period was extended up to nine days with the use of pentaerythritol. Moreover, initial burst phase of drug release could be decreased incorporating pentaerythritol into the polymer.

Figure: 5.5 Total release diclofenac from a) glycerol and b) pentaerythritol containing co-polymers of lactic acid and citric acid.
5.8.3 Equilibrium swelling ratio:

The results shown in figure 5.3 indicate that the swelling ratio for the copolymers in phosphate buffer pH 7.4 are in the order of G1>G2>G3. In other words, the greater is the content of the glycerol, the lower is the swelling ratio because of the more number of free -OH functional groups and thereby increasing the hydrophilicity. Copolymer G3 starts degrading hydrolytically after 7.5 hs and dissolved completely at 70 hr. After 95 hr G2 started degrading whereas G1 was stable even after 119 hr (Fig. 5.6a).

![Swelling ratio as a function of time for a) glycerol and b) pentaerythritol containing co-polymers of lactic acid and citric acid.](image)

Copolymers of pentaerythritol were quite stable that of glycerol. Larger swelling ratio was obtained with P2 followed by P1 and P3. Unlike glycerol containing copolymers, copolymers of pentaerythritol showed hydrolytic degradation in the order, P1>P2>P3. Onset of degradation for P1 was 97 h and for P2 and P3 were 168 h and 198 h, respectively (Fig. 5.6b). Hence drug release study was discontinued after any one polymer degrades completely.

5.8.4 Swelling kinetics:

Swelling results showed that higher the swelling ratio, higher is the rate of water penetrating into the copolymer. Based on the relative rates of diffusion and polymer relaxation, Alfrey et al (1996) have distinguished three classes of diffusion.

1. Fickian diffusion (n≤0.5):

   Here the rate of diffusion is much smaller than that of relaxation of entangled polymer chains. In this case the system is controlled by diffusion phenomenon.
2. Case II (n=1.0)

This is the case of other extreme to the fickian diffusion, where the diffusion process is very fast compared to relaxation of polymer chains. The controlling step here is the velocity of an advancing front of solvent, which forms the boundary between swollen polymer and a glassy core.

3. Non-fickian diffusion (0.5<n>1.0)

In this case rates of diffusion and relaxation are comparable.

As revealed from the swelling data presented in the table 5.3, transport mechanism in all the glycerol containing polymers can be classified as non fickian transport and for polymers P1 and P2 as non fickian transport and that of P3 can be classified as Fickian (Fig. 5.7).

<table>
<thead>
<tr>
<th>Sample code</th>
<th>Equilibrium swelling ratio (g/g)</th>
<th>(n)</th>
<th>(\kappa)</th>
<th>Density of polymer (p)</th>
<th>(V_p) in the swollen state</th>
<th>Mol.Wt. between two cross links (M_c)</th>
</tr>
</thead>
<tbody>
<tr>
<td>G1</td>
<td>24.0</td>
<td>0.7458</td>
<td>0.0796</td>
<td>1.005</td>
<td>0.0708</td>
<td>2020.5</td>
</tr>
<tr>
<td>G2</td>
<td>18.9</td>
<td>0.6477</td>
<td>0.1033</td>
<td>1.005</td>
<td>0.0714</td>
<td>9888.0</td>
</tr>
<tr>
<td>G3</td>
<td>17.3</td>
<td>0.6952</td>
<td>0.1287</td>
<td>1.005</td>
<td>0.065</td>
<td>10340.8</td>
</tr>
<tr>
<td>P1</td>
<td>13.4</td>
<td>0.6205</td>
<td>0.1000</td>
<td>1.01</td>
<td>0.0656</td>
<td>10376.5</td>
</tr>
<tr>
<td>P2</td>
<td>15.6</td>
<td>0.6465</td>
<td>0.0639</td>
<td>1.01</td>
<td>0.0594</td>
<td>11518.0</td>
</tr>
<tr>
<td>P3</td>
<td>7.6</td>
<td>0.4533</td>
<td>0.1572</td>
<td>1.00</td>
<td>0.2328</td>
<td>878.3.0</td>
</tr>
</tbody>
</table>

Table: 5.3 Swelling properties of the co-polymers

5.8.5 Characterization of copolymers:

Molecular weight of the copolymers was calculated on the basis of the swelling properties as described in materials and method. It was observed that as molar ratio of the monomer increases, the molecular weight of the copolymer increases except copolymer P3. From the swelling ratio and swelling behavior, it could be concluded that higher molecular weight of the copolymer results in the faster hydrolytic degradation and solubilization of the copolymers as in the case of G1, G2, G3, P1 and P2. Most stable copolymer is P3 and its molecular weight is the lowest among the P copolymers (table 5.3).
Figure: 5.7 Plots of ln Qt/Qinf versus ln t of copolymers: a, G1; b, G2; c, G3; d, P1; e, P2 and f, P3.

DSC analysis of the copolymer G exhibits that $T_g$ of the copolymers increases as monomer ratio increases and thermal degradation of the polymers occurs in single step. Moreover it does not melt before the thermal degradation starts as will be the case in other polymers (PHA). Copolymer G was stable up to the temperature of 200 °C. Inverse is the case with the copolymers P, where $T_g$ of the polymer decreases with
Lactic acid co-polymers and sustained drug release-128

increase in the monomer ratio and thermal degradation proceeds in two steps. Theses copolymers were stable up to 200 °C (table 5.4, Fig. 5.8 and 5.9).

<table>
<thead>
<tr>
<th>Copolymer</th>
<th>Tg °C</th>
<th>Td</th>
<th>% weight loss</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>100 °C</td>
<td>200 °C</td>
<td>300 °C</td>
</tr>
<tr>
<td>G1</td>
<td>249.73</td>
<td>185.72</td>
<td>0.31</td>
</tr>
<tr>
<td>G2</td>
<td>257.91</td>
<td>189.29</td>
<td>0.42</td>
</tr>
<tr>
<td>G3</td>
<td>264.42</td>
<td>204.46</td>
<td>0.78</td>
</tr>
<tr>
<td>P1</td>
<td>254.13</td>
<td>185.36</td>
<td>3.43</td>
</tr>
<tr>
<td>P2</td>
<td>246.46</td>
<td>177.68</td>
<td>3.64</td>
</tr>
<tr>
<td>P3</td>
<td>239.87</td>
<td>201.78</td>
<td>2.59</td>
</tr>
</tbody>
</table>

Td - temperature at which degradation starts

Table: 5.4 Thermal properties of copolymers
Figure: 5.8 DSC thermogram of copolymers

Figure: 5.9 TGA analysis of copolymers

Figure: 5.10 FTIR spectrum of copolymers G and P
FTIR analysis of the copolymers showed the presence of the following groups: 1064 cm\(^{-1}\) C=O stretching, 1370 cm\(^{-1}\) C-H symmetric stretching, 1475 cm\(^{-1}\) C-H asymmetric stretching, 1736 cm\(^{-1}\) C=O stretching for ester, 2345 cm\(^{-1}\) broad band for H bonded –COO (Fig. 5.10).

5.9 Conclusion:

Lactic acid was successfully used for the preparation of copolymers with citric acid and glycerol / pentaerythritol. Drug release could be sustained for 4 days with glycerol and for 9 days with pentaerythritol containing copolymers with simultaneous dissolution of polymer.

The advantage of this drug delivery system is that it does not involve any harsh conditions for entrapment of the drug into the polymer due to which drug may losses its activity. As discussed, earlier lactic acid based polymers are biocompatible and make this device a potential system for delivery of molecules in pharmaceutical industry. Another advantage is that, duration of release of drug can be easily adjusted by changing the monomer and by just adjusting the monomer ratio.
5.10 References:


