SYNTHETIC STUDIES OF POLYMER AS A DRUG CARRIER

(A DISSERTATION REPORT)

By

Ms. SNEHA D. GAWDE

(20P0490033)

SCHOOL OF CHEMICAL SCIENCES

GOA UNIVERSITY

GOA 403206

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Ms. Sneha D. Gawde

(20P0490033)

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CERTIFICATE

This is to certify that the dissertation entitled **"SYNTHETIC STUDIES OF POLYMER AS A DRUG CARRIER"** is bonafide work carried out by Ms. Sneha Devanand Gawde under my supervision in partial fulfilment of the requirement for the award of the degree of Master of Science in Chemistry at the School of Chemical Sciences, Goa University

Prof. Dr. Vidyadatta Verenkar
(Guiding Teacher)
Dean of School of Chemical Sciences
Goa University

Sneha D. Gawde
(M. Sc. Student)

DECLARATION

I hereby declare that the work presented in this dissertation report entitled **"SYNTHETIC STUDIES OF POLYMER AS A DRUG CARRIER"** is based on results of investigation carried out by me in the School of Chemical Sciences, Goa University, Goa under the supervision of Dr. Diptesh Naik and the same has not been submitted elsewhere for the award of a degree or diploma.

Sneha D. Gawde

20P0490033

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INTRODUCTION

The pharmaceutical applications of polymers span largely from their use as binders in tablets and capsules to viscosity and flow controlling agents in liquids and emulsions. Use of polymer is now broadened to controlled release and focused on drug delivery system. Polymers are acquired from natural source as well as produced synthetically. Biodegradable

and non-biodegradable are two broad classes of polymer. Biodegradable polymers have been largely used in biomedical purposes due to its biocompatible and biodegradable nature. This assessment gives brief overview on distinct biodegradable polymers that are presently being used in the evolution of controlled drug delivery system. [1]

Drug delivery is the approach or technique of administering pharmaceutical compound to obtain a therapeutic impact in human beings or animals. Drug delivery technologies manage study related to drug release, consumption, diffusion and eradication for the advantage of enhancing product efficiency, well being, as well as patient adherence and satisfaction. Controlled drug delivery science represents one of the most swiftly advancing areas of science in which chemists and chemical engineers are devoting to human fitness care. Such delivery systems provide with countless benefits contrast to conventional dosage types including elevated efficiency, reduced harmful effect, and increased patient conformance. Such systems prefer synthetic polymers as drug carrier. [2]

Advantages of controlled release system

Controlled release system has a range of advantages over conventional release system as given below: Improved drug steadiness, decreased complexity of drug, reduction in doses, increased adaptation, and better efficiency of drug, refined bio accessibility of drug, more economical.[3]

Classification of Polymers

Polymers are categorised into the two fundamental kinds as mentioned below. [4]

- Natural polymers

Protein-based polymer	Collagen, Albumin, Gelatin
Polysaccharides	Alginate, Cyclodextrin, Chitosan, Dextran, Agarose, Hyaluronic acid, Starch, Cellulose

- Synthetic polymers

Biodegradable polymers

Polyester	Poly lactic acid, Poly glycolic acid Poly hydroxyl butyrate, Polyester, Polycaprolactone, Poly lactide-co-glycolide (PLGA), Poly diaxonone
Polyanhydride	Poly adepic acid, Poly sebacic acid Poly terpthalic acid
Polyamides	Poly amino acid, Poly imino carbonate
Phosphorous based polymer	Polyphosphates, Poly phosphonates, Poly Phosphazenes
Others	Poly cyanoacrylates, Poly urethanes, Poly ortho ester, Polyacetals etc.

Non-Biodegradable polymers

Cellulose derivative	Carboxy methyl cellulose, Ethyl cellulose, Cellulose acetate hydroxyl propyl methyl cellulose
Silicons	Polydimethyl siloxane, Colloidal silica, Polymethacrylate, Polymethyl methacrylate
Others	Poly vinyl pyrolidine, Ethyl vinyl acetate, Poloxamine etc.

Why synthetic polymers favoured over natural polymers?

Natural polymers are prone to some disadvantages as outlined below:

Microbial contamination - Normally 10% or more moisture is found in gum and mucilages and structurally they are carbohydrates and at some point of production, they are uncovered to the exterior surrounding and so there is a chance of contamination due to microorganisms.

Batch to batch variation-Synthetic production is a controlled method with stable amount of ingredients, whilst the production of gums and mucilages is dependent on environmental and continual factors.

Uncontrolled rate of hydration- The percentage of chemical elements present in a given material may vary depending on changes in natural substances and variations in region, species, and local climate. Suitable composition must be used on available gums and

mucilages. Normally on storage reduced viscosity is needed, but viscosity of the formulations increases when gums and mucilages come in contact with water. Since nature of gums and mucilages (monosaccharides to polysaccharides and their derivatives) is complex, it has been seen that there is reduction in viscosity after storage.

Synthetic polymers help to overcomes above disadvantages and for this reason they are preferred in formulation. [5]

Considerations for Selection of Polymers

Thorough understanding of the surface and bulk properties of the polymer provides suitable chemical, mechanical, interfacial and organic properties. The choice of polymer depends on Physico-chemical properties, biochemical characterisation, and preclinical test. Properties such as hydrophilicity, lubricity, smoothness and surface energy determine the biocompatibility of polymer with blood and tissues. In addition to it durability, permeability and degradability influence physical properties. Water sorption capacity of the polymers is determined by surface properties. Bulk properties such as molecular weight, adhesion, solubility decides release mechanism. Structural properties, micromorphology and pore dimension are important with respect to mass transport (of water) into and (of drug) out of the polymer. For non-biodegradable matrices, release of drug is diffusion-controlled and peptide drugs which has low permeability is launched through the pores and channels created. Non-toxicity, versatility, good physical and chemical properties with outstanding mechanical strength, easy to construct, less costly, inert, and consistent with surrounding are some characteristic a polymer should possess to be used for CDDS.[6]

Synthetic Biodegradable Polymers

Synthetic biodegradable polymers are presently being considered as drug delivery systems or as platform for tissue vascular orthopaedic, skin adhesive and surgical glues. Polymer materials having physical, chemical, biological, and biomechanical properties to grant efficient therapy are mostly in demand. As a consequence, a range of degradable polymers, both natural and synthetic, have been studied for these applications. Nonetheless natural polymer composition varies source to source. [7]

Advantages of Biodegradable Polymers as Drug Carrier

The advantages of Biodegradable polymers as drug carriers include: localized and sustained delivery of drug, stabilization of the drug, limited and regular release rate with time, ability to tailor degradation rate and mechanical property, ability to be designed into various shapes.[8]

AIM & OBJECTIVE

Aim – Synthetic study of biodegradable polymer as drug carrier.

Objective – To investigate synthesis methods of biodegradable synthetic polymer which can be used as drug carrier.

ABSTRACT

Applications of controlled drug delivery systems have been major area of research in pharmaceutical studies. There is increase growth in therapeutic index due to targeting of drugs to a particular tissue. Polymers play a vital role in the development of drug delivery systems by providing controlled, unaffected and targeted release of drug. Application of bio medical materials focuses on less harmful and good bio compatible biodegradable polymers. This review describes the synthetic studies of bioresorbable polymers such as Polylactic acid (PLA), Polyglycolic acid (PGA), Polyhydroxybutyrate (PHB), Polyanhydride and Polyaminoacid (PAA). Drug release rate and duration of release depends on meticulous selection of polymer. Polymers occur naturally and can even be produced synthetically. One important factor to consider for selection of polymer is interaction between drug and polymer this in turn decides the mechanism of drug release and properties of selected polymer will influence the release rate.

LITERATURE REVIEW

Synthetic Biodegradable Polymers for Drug Delivery System

1) **Polylactic acid (PLA)**

A higher-molecular-weight polylactic acid was synthesised by DuPont in 1954 and had applied for a patent. Society had given major attention to research on polymers. Therapeutic and general health started progressing in the 1960s and polylactic acid was being used in surgical sutures and bone implants. Now, FDA and European regulatory authorities has permitted PLA resin to be use in food- and drug-delivery systems. Auras et al. suggested three methods for the synthesis of polymer PLA (Mw > 10,000): direct condensation polymerization, azeotropic dehydration condensation and lactide ring-opening polymerization, as shown in Figure 1.[9][6]

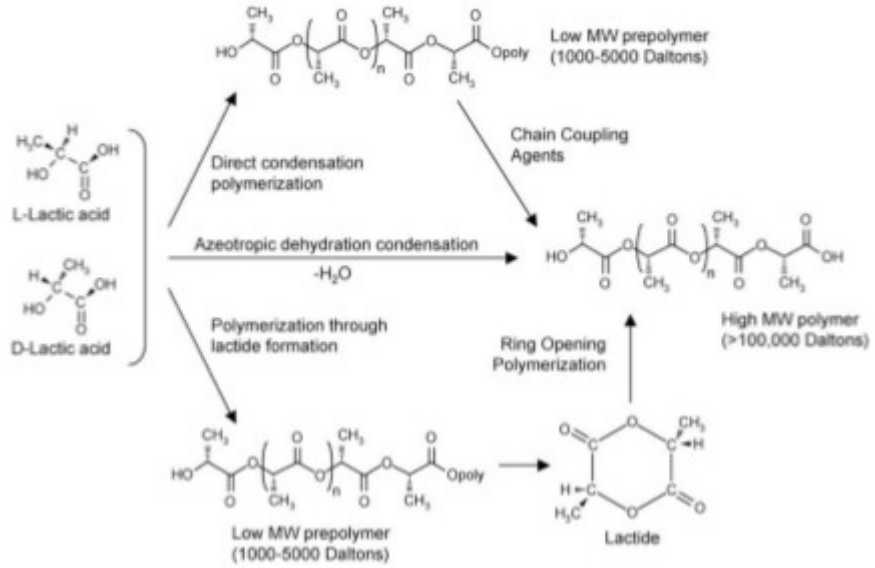

Figure 1: Synthesis of polylactic acid (PLA) from L- and D-lactic acids

PLA can be broken down into LA which is metabolized by the human body. FDA has approved this for biomedical use. In the 1970s, Yolles et al. used PLA for research to synthesise a PLA complex containing naltrexone. At 35 days the in vitro release rate was 67% .The blocking effect on morphine due to the complex was verified by in vivo experiments. Ruan et al. synthesised PLA–PEG–PLA microspheres containing paclitaxel using PLA copolymers. The invariable dimension and porous structure of the prepared microspheres promoted drug release. At 30 days In vitro release reached 49% extending drug processing time and improving its efficiency. Inconsistent local accumulation due to drug release was eluded using this sustained-release drug delivery system, thus increasing the therapeutic result. The benefits of this slow-release “smart” drug-delivery system include: less side effects of drugs on the gastrointestinal tract and within a given duration high concentration of drug was eluded, which might lead to allergies or harmful effects. Also, degradable materials can be broken down in specific environments.[6]

2. Polyglycolic acid (PGA)

Poly (glycolic acid) was synthesis of using a stirred reactor by Jigang et al. to set up an industrial approach for synthesis of poly (glycolic acid). They had determined correlation between the change in intrinsic viscosity and monomer conversion rate and thermal steadiness of polymer during polymerization process. Poly (glycolic acid) was synthesised with the aid of direct melt polymerization by Zhaoyang et al. In their work, they had used

direct melt polymerization method to obtained poly (glycolic acid) at 165 degree celsius and 70 Pa for 10 hours using catalyst (tin bichloride) and characterisation was done via IR, DSC and X-ray diffractometry. The poly (glycolic acid) synthesised by this method had high crystallinity and crystallite size. Enomoto et al. suggested a direct method for synthesis of poly (L-lactic-acid) by using melt polycondensation in continuous microwave radiation.

Ring opening polymerization was another method reported by Carothers in 1932 to obtain low molecular weight polymer. Finally in 1950s high molecular weight polylactones was produced using ring opening polymerization techniques due to effective monomer purification techniques.

Synthesis of homopoly (glycolic acid) from glycolide was carried out using ring opening polymerization as mentioned by Leenslag and Pennings using exclusive catalysts. They also evaluated the consequence of o monomer purity, concentration of catalyst and polymerization time.[10]

3) Polyhydroxybutyrate

Polyhydroxybutyrate nanoparticles was synthesised by P. Senthilkumar et al. for the application hydrophobic drug delivery. They fulfil most of the requirement as a drug carrier. In this study, nanoprecipitation method with solvent systems i.e. Chloroform: DMSO (CD), Chloroform: Water (CW), Ethylacetate: DMSO (ED) and Ethylacetate: Water (EW) was used to synthesis surfactant (Span20) influenced PHB nanoparticle loaded with a hydrophobic drug -curcumin. Further, using this in-vitro drug release studies were carried out. The dimensions of nanoparticles were below 300nm in size and these nanoparticles had been determined to launch the drug for longer period. When solvent (acetic acid) was used it was found that the nanoparticles efficiently released the encapsulated drug (curcumin) from the study carried out against Bacillus subtilis[11]

4) Polyanhydride

Polyanhydrides polymers are formed by the linkages of anhydride bonds between repeat units. Surface-eroding polymers such as Polyanhydrides exhibit hydrolysis rate faster than diffusion rate. As a result, erosion takes place on the outer surface of the polymer, which maintain polymer backbone’s structural integrity throughout the degradation process . Degradation is well controlled due to surface erosion. The hydrophobicity of the polymer and hydrolytically labile anhydride linkage controlled release profile of bioactives from

polyanhydride-based systems. Depending on the polymer chemistry the hydrolytic degradation lasts days or months. Polyanhydrides generally degrade to their acid counterparts as noncytotoxic products verified based on biocompatibility studies, both in vitro and in vivo.Hence, they are used in biomedical applications such as in drug delivery and implant biomaterial. Stéphan Bien-Aimé and Kathryn Uhrich had developed techniques to synthesis of Polyanhydride which are employed for the synthesis of polyanhydrides.

5) Polyaminoacids

Polyamide is formed when repeating units of polymer is linked by amide bonds and polyamides are formed by linking multiple amino acids of the same types via amide bonds such as nylons, sodium poly(aspartate) and aramids . Polyamides can also be classified into: homopolyamides and copolyamides. In 1938, DurationPont first presented polyamide as the toothbrush filaments . By 1950, it was used in the plastic industry due to its properties such as thermal stability, good chemical resistance, relatively high tensile strength and stiffness.

Polyamides possess excellent mechanical characteristics, good sliding and wearing characteristics. Polyamides are of two types PA 66 (hard and tough) and PA 12 (soft with flexible properties). In the 2000s, polyamide polymers found application in water-insoluble and metabolically unstable anti-neoplastic drugs. The benefits of using polyamide polymers as the drug delivery system include localized target site action, sustained release and stabilization. Aliphatic polyamides complexed with nanoparticles have been utilized for multifunctional applications. [12]

PAA can carry versatile reactive functional groups at their side chains (carboxylic acids, hydroxyl, amino and thiol groups). These render PAA and polypeptides excellent polymers for drug delivery (DD) applications. Traditionally, amino acids have been polymerized by conventional solid-phase peptide synthesis. A large number of oligomers and short peptides can be easily synthesized by this well-established method. However, the preparation of peptides larger than 100 residues usually results in undesired by-products due to incomplete deprotection and coupling steps. To date, various alternative approaches to produce PAA and their block copolymers have been developed.

METHODOLOGY

1.Polylactic acid

Polylactic acid is comprised of a monomer of lactic acid. There are two optical isomers of lactic acid, L-lactic acid and D-lactic acid. Forms in which polylactic acid are produced include poly-l-lactic acid (PLLA), poly-d-lactic acid (PDLA), and poly-d,l-lactic acid (PDLLA). α, β, and γ are three forms in which polylactic acid can be crystallised. Initially lactic acid was produced from fermentation of sugars (starch, glucose, lactose,and maltose) by bacteria. Fermentation process is carried out under pH (about 5.0) and low oxygen at 40 degree Celsius for 3-5 days.But with increase in concentration of fermented lactic acid, toxicity is produced and therefore to obtain high degree of lactic acid, purification methods

are employed. Chemical synthesis methods of lactic acids includes (a) The lactonitrile method. To obtain crude LA, Lactonitrile is reacted with water in presence of sulfuric acid. For esterification the crude LA is mixed with ethanol, and by using distillation, concentration, and decomposition refined lactic acid is synthesised. (b) The acrylonitrile method. Here, acrylonitrile replaces lactonitrile, hydrolyzed with sulfuric acid. Then, the hydrolyzed product is reacted with methanol; the crude ester is sent to distillation and the refined ester is heated and vacuumed to obtain the product. (c) The propionic acid method.Here, propionic acid is used as raw material, crude lactic acid is obtained via chlorination and hydrolysis and the product is obtained through esterification, rectification, and hydrolysis. [13]

Low-molecular-weight polylacticacid

To produce low-molecular-weight polylacticacid, dehydration condensation of hydroxyl and carboxyl groups is carried out at at equimolar concentrations. Next, coupling agents and esterification adjuvants is added. To remove the adjuvant and byproducts in the reaction triphosgene is added. The azeotropic dehydration condensation method avoids the use of adjuvants during the synthesis of PLA. First, lactic acid is distilled under reduced pressure at 130◦C for 2–3 h to remove condensed water. The catalyst and diphenyl ether are added to the reaction. This is passed through a molecular sieve and returned to the container for another 30–40 h at a temperature of 130◦C. The polymer can then be separated or dissolved and precipitated for further purification.[6]

High-molecular-weight PLA

The ring-opening polymerization of lactide is another methods for production of high-molecular-weight PLA. Lactide has three stereo configurations—l-lactide, mesolactide, and d-lactide. formed by solvent-free dehydration under mild conditions.Once high-purity lactide are obtained ,depending on the catalyst the ring-opening polymerization of lactide follows one of three mechanisms: cation, anion, and coordination/insertion[6]

2. Polyglycolic acid

The following strategies are used to prepare poly (glycolic acid).

a) Low Molecular Weight PGA Synthesis

Direct Polycondensation Polymerization of Synthetic Glycolic Acid.

Glycolic acid is subjected to heat at atmospheric pressure and a temperature of about 175–185◦C is maintained till water ceases to distill. After that, pressure is decreased to 150 mm Hg, still maintaining the same temperature for about two hours and the low molecular weight poly (glycolic acid) is synthesised. The polymer synthesised has a low molecular weight, because it is hard to drain water from viscous reaction mixture. In the polycondensation system of PGA, two foremost equilibrium exist: a- dehydration equilibrium for esterification Figure 2 and b- ring chain equilibrium involving depolymerization to glycolide Figure 3.[10]

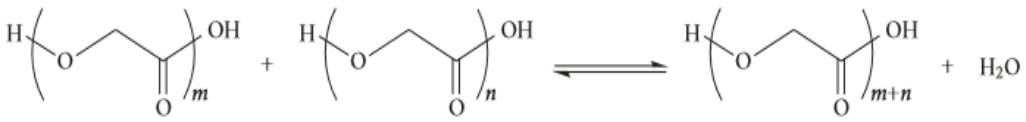

Figure 2: Polycondensation - dehydration equilibrium for esterification

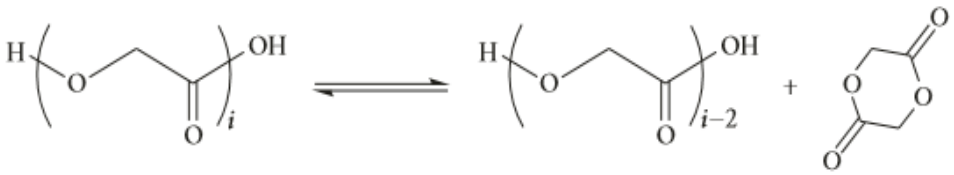

Figure 3: Polycondensation - ring chain equilibrium involving depolymerization to glycolide

b) High Molecular Weight PGA Synthesis.

Azeotropic Condensation Polymerization of Glycolic Acid.

High molecular weight is synthesised azeotropically. In this method, the trouble of the elimination of water is overcome by controlling the equilibrium between a monomer and a polymer in an organic solvent and thus glycolic acid is polycondensed at once into a polymer. The technique used is solution polymerisation, here low boiling organic solvent and high activity catalyst is used. Water as a derivative is removed azeotropically, whereas solvent (dried) is recycled back in the reaction. The reaction temperature must be beneath the melting point of polymer; this prevents depolymerization and racemisation throughout polymerisation.[10]

3 Polyhydroxybutyrate

Drug Encapsulation Efficiency

The curcumin loaded nanoparticles, were aspirated with 1ml of the supernatant after centrifugation at 5000 rpm. This was performed after every 10 minutes and absorbance was recorded at 421nm using UV visible spectrophotometer (Systronics), absorbance maxima of curcumin was 421nm. A plot of absorbance verses time was used to find the efficiency of the nanoparticles to encapsulate the drug with respect to time.[10]

In Vitro Drug Release Kinetics

Dialysis method was used to check the ability of the nanoparticle to release the encapsulated drug. Dialysis membrane coated with a suspension of nanoparticle in PBS (pH 7) in the ratio 0.5:1 used to be positioned in acidic PBS solution (pH 3) at room temperature and after every 10 min, 1 ml of solution was collected up to 180 min. The absorbance of curcumin measured using UV visible spectrophotometer (Systronics) at a wavelength of 421nm. A graph of absorbance verses time was plotted.

In-Vitro Controlled Release Studies

Here, agar well diffusion method was used. The nanoparticles were dissolved using solvents- PBS (pH 7) or acetic acid (1%). Nutrient agar plates had been swabbed all over with Bacillus subtilis and wells have been bored. Different concentrations (2, 4, 6, 8µg/ml) of nanoparticles dispersed in respective solvents were introduced to the wells. Erythromycin was once used as advantageous manage and the respective solvent as a bad control. The plates were incubated for 24h and the area of inhibition was recorded.

Drug Encapsulation Efficiency

After characterization, the nanoparticles were utilized for curcumin encapsulation. The nanoparticles were found to encapsulate the curcumin in a steady fashion except for the nanoparticles fashioned using chloroform- DMSO. Encapsulation used to be found to be increasing as time length increased. Nanoparticles organized the use of Chloroform – Water, encapsulated drug effectively and better. Surfactants were reported to decorate the drug loading efficiency. In a study, it used to be located that the encapsulation of curcumin into

PHA nanoparticles was slower when surfactant was not used. Shakeriet al has loaded lipophilic carvocrol into PHB primarily based nanoparticles and the loading efficiency used to be observed to be 21%.

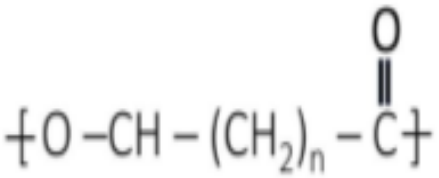

Figure 4: General structure of Polyhydroxybutyrate

4 Polyanhydride

Ring-opening polymerization (ROP)

During ROP in the presence of an anionic or cationic initiator a cyclic anhydride undergoes ring cleavage and undergoes polymerisation to form larger polymaerchain. For instance, poly(adipic anhydride) can be prepared from cyclic adipic anhydride using aluminum trichloride (cationic) or sodium hydride (anionic) initiators (Fig.5) . Condensation of diacids and acyl dichlorides is another technique, to prepare polyanhydrides (Fig.6). The reactants are dissolved in dichloromethane, in the presence of a base (i.e., triethylamine) and cooled in an ice bath. The rapid reaction of carboxylates with acyl chlorides typically results in complete polymerization within an hour.

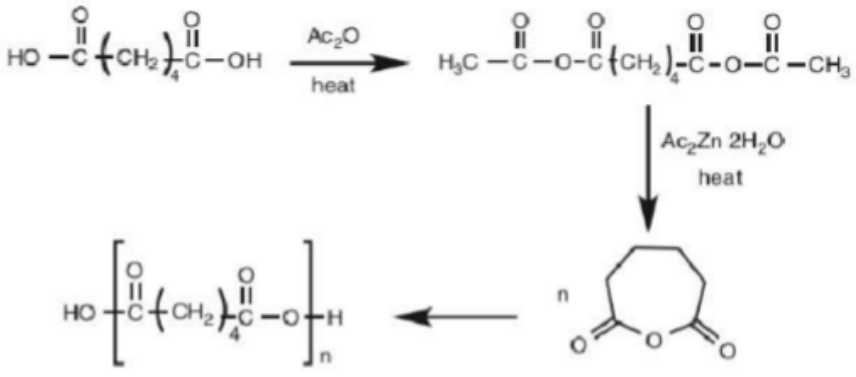

Figure 5: Synthesis of poly(adipic anhydride) from cyclic adipic anhydride monomer by ROP

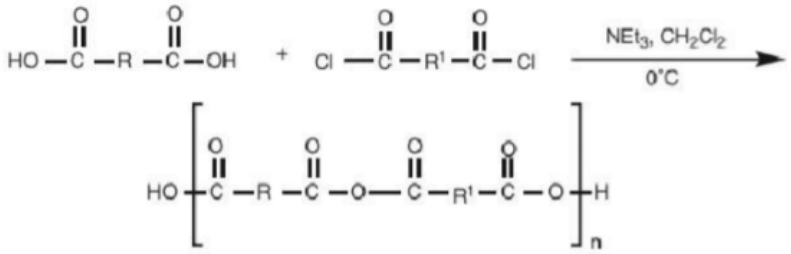

Figure 6: Condensation of diacids and diacyl chlorides to form polyanhydride copolymers

5. Polyamino acids

Ring opening polymerization (ROP)

The a-amino acid-N-carboxyanhydrides (NCAs) is the most commonly applied technique (Fig. 7). This method gives good yield and large quantity. Nucleophiles and bases such as primary amines or alkoxide anions are used as initiators to polymerise NCA. There is no identified universal initiators and polymerization conditions. Fine-tuning is required for optimum results. The most suitable amino acids for NCA preparation and polymerization are aspartic acid, glutamic acid and lysine. Presence of side reactions limits NCA polymerization due to broad molecular weight distributions.

The ‘amine’ and the ‘activated monomer’ (AM) mechanisms (Fig. 8).

The amine mechanism isbased on a nucleophilic ROP initiated by species with stronger nucleophilic like primary amines. In the AM mechanism, the NCA is deprotonated to become the nucleophile that initiates chain growth. It is attributed to strong bases such as metal alkoxides or tertiary amines. During polymerization a given system can switch back and forth between the amine and AM mechanism which results in side reactions. As a result, block copolymers prepared from NCAs like amine initiators show structures different from predicted and a considerable homopolymer contamination. These potential side reactions in the polymerization of NCAs have made the synthesis of PAA with controlled molecular weight and low polydispersity unsuccessful until 1997, when Deming discovered novel NCA initiators based on transition metal complexes. In 2004 Hadjichristidis and co-workers reported the preparation of PAA with control over chain length and length distribution under high-vacuum conditions. Also in 2004, Olivia Giani and co-workers lowered the temperature of the polymerization process to 0°C as a strategy to obtain well-defined PAA. Another

innovative strategy to control amine-initiated NCA polymerizations has been described by Schlaad and co-workers, who employed primary amine hydrochloride salts as initiators to obtain well defined PAA segments of narrow chain length distribution (Mw/Mn < 1.03). More recently, Lu and co-workers have reported on the controlled living polymerization of NCAs mediated by hexamethyldisilazane (HMDS). These authors have identified trimethylsilyl carbamate (TMSCBM) as an efficient chain-propagating group and demonstrated that alternative TMS-protected amines were also efficient initiators, allowing the introduction of different functionalities for further chemical transformations, including 'click reactions'

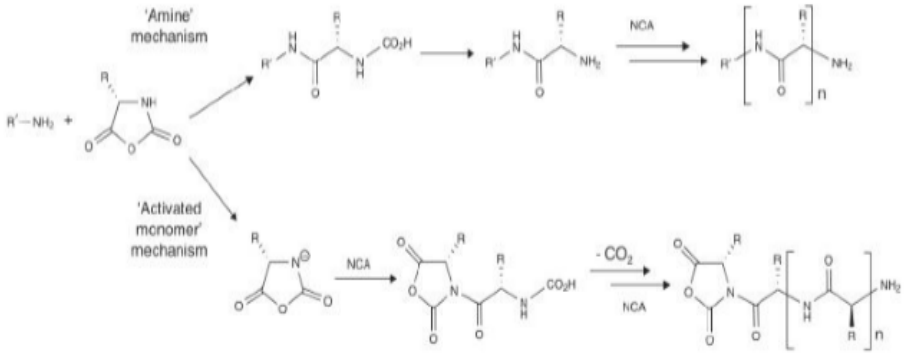

Figure 7: Ring-opening polymerization of a-amino acid-N-carboxyanhydrides (NCAs)

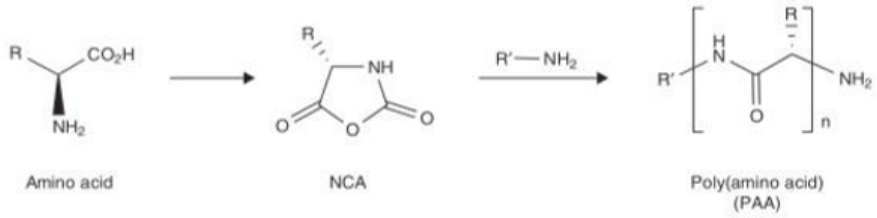

Figure 8: 'Amine' and 'activated monomer' mechanisms

CONCLUSION

Polymers are macromolecules having very large chains comprise a range of functional groups, can be blended with low and high molecular weight materials. Polymers are becoming more and more vital in the area of drug delivery. Advances in polymer science have led to the improvement of quite a few novel drug delivery systems. Use of polymer systems for the delivery of therapeutics, bioactive materials, and even genetic material has minimized several issues to a great extent like bioavailability problems, high dosing frequency, environmental and biological instability, etc.

Polymers possess a unique strength in their application towards drug delivery systems which enables the new advancement in the formulation of new drug delivery systems which improves the therapy and treatment. Biodegradable polymers have proven their potential for

the development of new, advanced and efficient drug delivery system. They are capable of delivering a wide range of bioactive materials. From a polymer chemistry perspective, it is important to appreciate that the mechanisms of controlled-release require polymers with a variety of physico-chemical properties. Several types of polymers have been investigated as potential drug delivery systems, including Nano and microparticles, dendrimers, Nano and micro-spheres, capsosomes and micelles. In these systems, drugs can be encapsulated or conjugated into polymer matrices to control the drug release. Studies show that the near future will definitely be instrumental for the development of new polymers, which can be seen in the development of molecularly imprinted polymers

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