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Bio-absorbable polymers in implantation-An overview

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Poly-α-hydroxy aliphatic esters are novel bio-absorbable polymers (BAPs), which are being used extensively as implantation products (orthopaedics, drug delivery, scaffolds and sutures). Polylactic acid (PLA), polyglycolic acid (PGA) and polydioxanone (PDO) are approved from food and drug administration agency (FDA) for human clinical uses. This review presents available synthetic routes for making bio-absorbable polymers, their properties and end use applications.

Keywords: Bio-absorbable polymer, Polylactic acid, Polyglycolic acid

Introduction

Orthopaedic surgeons have been repairing serious bone fractures by binding fractures with screws, pins, and other fixation-type devices using metals made up of highly sophisticated metal alloys of cobalt[1-4], titanium[5-7], zirconium[8-10], and tantalum[11-13]. However, these metal alloys are hard and stiffer than bone and possibly interfere with regenerating bones. Search for more compatible materials with the human body led to consider bio-absorbable polymers (BAPs). In 1960s, Kulkarni *et al*[14,15] implanted BAP as sutures and rod for repairing mandibular fractures in dog. Poly-α-hydroxyaliphatic esters are developed *in vivo* biomedical applications of orthopaedics, drug delivery systems, scaffolds, sutures and staplers. BAPs over alloys can eventually be resorbed or excreted by human metabolism without any side effects and exhibit more bone-like properties. Poylactic acid (PLA), polyglycolic acid (PGA) and polydioxanone (PDO) are some of the implant dominant BAPs (Scheme 1). Under ideal conditions, a BAP could encourage bone healing while body slowly metabolizes it, thus eliminating need for a second surgery that may be required when a metal alloy is implanted[15-20]. Polymeric drug delivery devices prevent drug degradation and may also provide management of drug release by varying drug-to-polymer ratio, molecular weight and composition of polymer[21,22]. Bio-absorbable implants can be designed for fracture fixation, drug delivery, or ligament repair and other clinical use.

This review presents current issues on methods of preparation of bio-absorbable materials using various catalysts and initiators for making high molecular weight and functional BAPs, besides structure-property correlations of polymers prepared under various conditions and their end use applipÎ:cations.

Preparation of Bio-absorbable Polymers (BAPs)

Polycondensation

Under polymerization of lactic acid and glycolic acid via direct condensation, hydroxyl group present in ±-position reduces reactivity of monomer and thereby increases reaction time. High purity is important to undergo effective reaction although commercially available monomer in the market is 85-90% pure[23-25]. Regular polycondensation method produces low molar mass products. Low molar mass oilgo (lactic acid) (OLA), oilgo (glycolic acid) (OGA) and combination of copolymers with functional monomers can be used to develop spherical microspheres for drug delivery systems and high molar mass polymers are also used for load bearing applications in biomedical implants[26-28]. Effect of catalytic action and method of polymerization plays an important role in synthesizing high molar mass polymers. Sn (II) and Ni (II) compounds show efficiency in synthesis of high molar weight polymers[29,30]. Stannous octoate and tetraphenyltin catalysts have been approved by Food and

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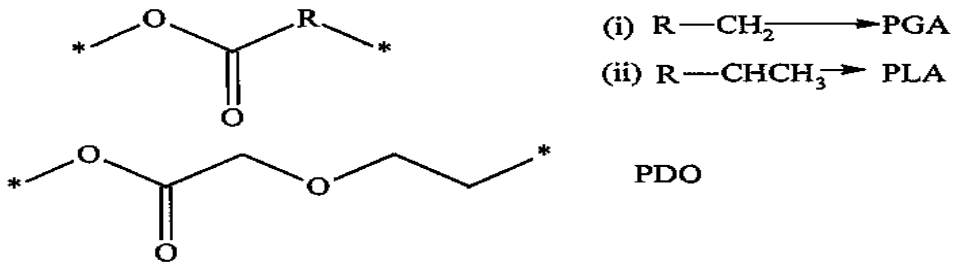
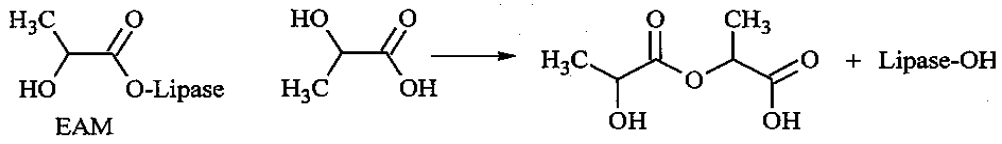


Scheme 1 — Repeating units of bio-absorbable polymers

Table. 1—List of catalyst and polycondensation conditions.

Monomer	Catalyst	Reaction Time h	Temp °C	Reduced pressure mmHg	Mw (x10^4)	PDI
LA[32]	Ti $(BuO)_4$-(0.1wt-%)	3/24	100/180	75/atm	0.5247	1.97
LA[32]	$Fecl_3$-(0.1wt-%)	3/24	100/180	75/atm	0.5226	1.64
LA[32]	H_3PO_4-(0.1wt-%)	3/24	100/180	75/atm	0.4518	1.58
LA[32]	$Alcl_3$-(0.1wt-%)	3/24	100/180	75/atm	0.2340	1.63
L-LA[51]	TNBT	1/3/7/40	180	atm/760/ 760>1/1	13	3.30
L-LA[33]	$Sc(OTf)_3$ (0.1 mol)	10/10/5	65/130/170	30/0.3/0.3	7.34	1.40
L-LA[33]	$Sc(NTf2)_3$ (0.5 mol)	10/10/5	65/130/170	30/0.3/0.3	2.05	3.00
L-LA[25]	Tetraphenyltin	6/15	190	atm	4.3	3.58
L-LA[25]	Tetra-n-butyldichlorodistannoxane	6/15	190	atm	2.47	3.85
D,L-LA[34]	$Sncl_2$: pTSA (1:1-1wt %)	3/7	60/165	NS	9.116	1.90
D,L-LA[34]	$Sn(Oct)_2$:pTSA(1:1-1wt %)	3/9	60/165	NS	9.464	2.00
OLLA[55]	GeO_2 (0.8wt %)	20	180	10	2.8	-
OLLA[55]	Sb_2O_3 (0.1wt %)	20	200	-	2.0	-
OLLA[55]	ZnO(0.1wt %)	20	200	-	3.6	-
OLLA[55]	Fe_2O_3 (0.1wt %)	20	200	-	2.0	-
OLLA[55]	Al_2O_3 (8.5wt %)	20	200	-	2.7	-
OLLA[55]	SiO_2 (0.8 wt %)	20	180	-	1.1	-
OLLA[55]	TiO_2 (0.8 wt %)	20	180	-	1.1	-
OLLA[55]	SnO (0.2 wt %)	20	180	-	5.0	-
OLLA[55]	$Sncl_2.2H_2O$ (0.4 wt %)	20	180	-	4.1	-
OLLA[55]	TSA (0.34 wt %)	20	180	-	1.7	-
OLLA[35]	bmimAc(0.05 mol kg^{-1})	10	170	2.25	1.28	1.30
OLLA[35]	emimBr(0.05 mol kg^{-1})	10	170	2.25	1.04	1.17
OLLA[35]	bbimLLA(0.05 mol kg^{-1})	10	170	2.25	1.06	1.35
OLLA[35]	eeimLLA(0.05 mol kg^{-1})	10	170	2.25	1.25	1.34
OLLA[54]	SnCl/TSA(1:1-4wt%)	2/10	105/150	0/0.5	32	3.40
OGA[50]	$Zn(CH_3CO_2)_2.H_2O$	1/4/20	190	150/30/atm	4.5	2.00

Drug Administration Agency (FDA). Protonic acids [methanesulfonic (MSA) and *p*-toluenesulfonic acids (*p*-TSA)] are found to be effective catalysts for esterification. Binary catalyst based on protonic acid and tin compound yields high molar mass product in solid state condensation[30,31]. Some of the synthetic parameters and catalytic systems result in high molar mass polymers (Table 1).



Scheme 2 — Enzyme activated polycondensation

Enzymatic polycondensation, which synthesizes polyester with easy removal of catalyst from polymer, is preferable for biomedical applications. Enzyme activates functional group of monomer and continues further condensation reaction with enzyme activated monomers (EAM) (Scheme 2). Origin of enzyme and feed ratios of monomers greatly influence microstructure of polymer and regiospeciûc polymerization can be carried out under appropriate conditions[36,37]. O'Hagan *et al*[38] and Binns *et al*[39] reported high molar mass aliphatic acid using lipase where byproduct (water) was removed by passing solvent through molecular sieves. Linko *et al*[40] prepared high molecular weight polyesters by removing water using vacuum. Uyama *et al*[37] proposed that regioselectivity is controlled to give linear polymers consisting of ±, É–disubstituted units at lower temperature, since enzyme activity shows poor conversion at higher temperature[41,42].

In chemical catalysis based solution condensation polymerization, rate is faster as boiling point of azeotropic solvent becomes higher due to continuous removal of water from reaction. This will enhance reaction since continuous recycling of solvent may carry some water into reaction and this may reduce molecular weight of polymers[43,44]. Ajioka *et al*[45,46] reported high molar mass (140 kDa) by drying solvent via molecular sieves and maintain water content (< 3ppm) for continues recycling solvent incessantly during reaction (20-40h). Moon *et al*[47] and Fukushima *et al*[48] achieved high molar mass (500-600 kDa) by melt–solid condensation catalyzed by a $SnCl_2 \cdot 2H_2O$/*p*-TSA binary system. In this condensation process, low molar mass is first prepared by traditional condensation, crystallized by heat treatment at 105°C for 1-2 h, and heated at 150°C for a further period of 30 h post solid condensation. Crystalline region increases in the system during heat treatment. At the same time, residual catalyst and dimers are transferred into amorphous phase. Further reaction of post solid condensation conducted in amorphous phase[49,50]. Chen *et al* [51] obtained high molar mass (130 kDa) via bulk polymerization at 180°C under reduced pressure using titanium(IV) butoxide (TNBT) as a catalyst. Nagahata *et al*[52] proposed microwave assisted bulk condensation using various catalysts and binary catalyst systems at 200°C under reduced pressure, resulting in moderate molar mass (16,000) with a broad PDI (3.5). In microwave assisted bulk condensation, reaction time can be shortened considerably when compared to conventional polycondensation [53]. However, chain fragmentation and dimer formation gradually reduces molecular weight in bulk condensation and increases PDI at higher temperatures. Melt-solid condensation reaction carried out at ≤150°C, chain fragmentation have been controlled and high molecular weight polymers are obtained in high yield and in short reaction time, compared to bulk polymerization[54-56].

Ring Opening Polymerization (ROP)

ROP of cyclic dimers has been examined to get high molecular mass and having specific micro structured polymers for biomedical applications using various metal initiators, organo metal complexes and metal free initiator systems. Carothers *et al*[57] reported that lactide can polymerize between 140-150°C and also observed that glycoside can polymerize with zinc chloride and can depolymerize into monomer under vacuum condition. ROP of cyclic dimers can be performed by four different mechanisms[58-62] (cationic, anionic, coordination-insertion and enzymatic polymerization). Cuiping *et al*[63] studied reactivity of rare earth initiators using lactide at 90°C in toluene and summarized catalytic efficiency as: La > Gd > Nd > Y > Er ($M_n \leq 54$ kDa).

Magnesium and zinc catalysts form M^{2+} salts with very similar ionic radii and these metals are essential for life. Mg, Zn, Li, Ca, Fe and lanthanides are biocompatible metal initiators and preferred catalysts for biomedical applications[64-72]. Heavy metal catalysts (Cd, Sn, Pb, Zr, Bi and Y) are not recommended for biomedical applications. Although Sn(II) (2-ethylhexanoate) is a general catalyst used to high molecular weight because of solubility in organic solvent, monomer and in melt state polymer. Sn(II) (2-ethylhexanoate) produces optically pure polylactide for biomedical applications and residual heavy metal ions are removed by post purification process[72,73].

Table 2—List of initiator and ROP condition

Monomer	Initiator	T °C	Time, h	η_{inh}	Mnx10^3	PDI	Solvent
D,L-lactide[79]	$Y(OCH_2CH_2OiPr)_3]_2$	RM	3.000	-	14.5	1.23	DCM
L-lactide[80]	$Al(OTf)_3$	100	6.000	-	4.30	1.38	In Air
L-lactide[80]	$In(OTf)_3$	100	6.000	-	3.50	1.12	In Air
L-lactide[80]	$Sc(OTf)_3$	100	24.00	-	0.84	3.77	In Air
L-lactide[80]	$Cu(OTf)_3$	100	24.00	-	0.80	2.76	In Air
L-lactide[80]	AgOTf	100	240.0	-	0.58	2.19	In Air
L-lactide[80]	$Mg(OTf)_3$	100	240.0	-	0.76	2.45	In Air
L-lactide[80]	$Y(OTf)_3$	100	240.0	-	0.94	3.18	In Air
L-lactide[80]	$La(OTf)_3$	100	240.0	-	0.90	2.57	In Air
L-lactide[80]	$Sm(OTf)_3$	100	240.0	-	0.96	3.86	In Air
L-lactide[80]	$Yb(OTf)_3$	100	240.0	-	1.16	2.94	In Air
D,L-Lactide[81]	(R)-SALBinaphtAlOCH$_3$	70	281.0	-	12.7	1.27	Tol
L-lactide[82]	[5-Cl-salen]AlOMe	RM	120.0	-	12.0	1.10	DCM
D,L-Lactide[82]	[5-Cl-salen]AlOMe	RM	120.0	-	12.0	1.10	DCM
rac-Lactide[83]	Aluminum/Schiff base initiator	70	8.950	-	22.3	1.04	Tol
rac-Lactide[84]	BuLi	20	0.667	-	45.0	1.60	THF
rac-Lactide[84]	Bu_2Mg	20	0.667	-	23.0	1.50	THF
D,L-lactide[85]	[{MeC(O)CHC(NCH$_2$-CH$_2$O)Me}AlCL$_2$/ CHO	70	18.00	-	15.86	1.15	Tol
L-Lactide[86]	Bu_2Mg	0	96.00	3.01	-	-	Tol + CE
L-Lactide[86]	BuMgCl	80	86.00	0.45	-	-	Tol
D,L-Lactide[87]	La	90	0.833	-	54.3	1.64	Tol
D,L-Lactide[87]	Gd	90	0.833	-	41.2	1.60	Tol
D,L-Lactide[87]	Nd	90	0.833	-	25.8	1.55	Tol
D,L-Lactide[87]	Y	90	0.833	-	8.90	1.41	Tol
L-Lactide[88]	Calcium dimethoxide	120	1.500		7.30	1.43	Bulk
L-Lactide[89]	Sn alkoxide	60	163.0	-	116	1.18	Tol
L-Lactide[90]	Creatinine	165	96.00	-	14.0	1.30	Bulk
L-Lactide[91]	Dibutyltin Dimethoxide	70	20.00	-	40.1	1.65	Tol
L-Lactide[92]	$FeCl_2$	150	192.0	0.40	-	-	Bulk
L-Lactide[92]	$FeGlyC_2$	150	192.0	0.5	-	-	Bulk
L-Lactide[92]	$FeLaC_2$	150	192.0	0.72	-	-	Bulk
L-Lactide[92]	$FeMand_2$	150	192.0	0.38	-	-	Bulk
L-Lactide[92]	$SnOct_2$	120	96.00	2.65	-	-	Bulk
rac-lactide[93]	2,2-Diethyl-propane-1,3-diamine	70	5.616	-	11.7	1.08	Tol
D,L-Lactide[94]	$Fe(OEt)_3$	130	48.00	-	61.4	1.66	Bulk
D,L-Lactide[94]	$Fe(OPr)_3$	130	48.00	-	50.8	1.68	Bulk
D,L-Lactide[94]	$Fe(O^iPr)_3$	130	48.00	-	33.4	1.73	Bulk
D,L-Lactide[94]	$Fe(OBu)_3$	130	48.00	-	20.7	1.92	Bulk
L-Lactide[95]	$C_{15}H_{25}AgClN_3O_2$	160	4.000	-	5.10	1.23	Bulk
L-Lactide[95]	$C_{15}H_{24}AuClN_3O_2$	160	4.000	-	5.40	1.17	Bulk
L-Lactide[96]	Ge	120	162.0	-	41.4	1.40	CB
L-Lactide[97]	HBG. OAc	120	18.00	-	20.5	1.07	Bulk
D,L-Lactide[97]	HBG. OAc	120	18.00	-	20.0	1.10	Bulk
rac-Lactide[98]	$[(THF)NaFe(O^tBu)_3]_2$	RT	7.00	-	61.5	1.49	CH_2 Cl_2
D,L-Lactide[99]	La(OiPr)3	21	0.500	-	21.9	1.20	DCM/Tol
D,L-Lactide[100]	Zn	140	21.30	-	9.5	1.40	Bulk

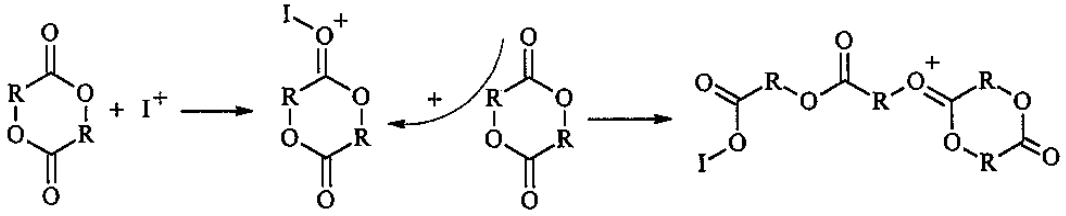
Contd.

D,L-Lactide[100]	Zn-lactate	140	11.90	-	105	1.70	Bulk
L-Lactide[101]	Zn(II) L-lactate	150	96.00	0.9	-	-	Bulk
L-Lactide[101]	Zn(II) L-mandelate	150	96.00	0.61	-	-	Bulk
L-Lactide[101]	Zn(II) stearate	150	144.0	0.68	-	-	Bulk
L-Lactide[101]	$ZnBr_2$	150	192.0	0.89	-	-	Bulk
L-Lactide[101]	ZnI_2	120	192.0	0.60	-	-	Bulk
L-Lactide[102]	Zn aceturate	150	192.0	0.65	-	-	Bulk
L-Lactide[102]	Zn prolinate	150	192.0	0.62	-	-	Bulk
L-Lactide[102]	Zn pyroglutamate	150	48.00	0.53	-	-	Bulk
L-Lactide[102]	Zn tosglycinate	150	96.00	0.52	-	-	Bulk
L-Lactide[102]	Zinc *N*-acetyl-4-aminobenzoate	150	48.00	0.59	-	-	Bulk
Gl: La: Cap[103]	Zirconium(IV) acetylacetonate	100	-	1.70	62.6	1.70	Bulk
L-Lactide[104]	Yttrocene complexes	25	70.00	-	44	1.20	CH_2Cl_2
D,L-Lactide[104]	Yttrium(III) Complexes	25	24.00	-	62.5	2.13	CH_2Cl_2
D,L-lactide[105]	Tetra(phenylethynyl)tin	0.25	140.0	-	599.9	1.91	Bulk
L-Lactide[106]	$Sn(OBu)_2$	19	120.0	-	968	1.36	Bulk
D,L-lactide[107]	2,6-dimethylaryloxide	100	0.750	-	36.1	1.59	Tol
L-Lactide[108]	Titanium Alkoxide Complex	130	12.00	-	15	2.33	Bulk
Lactide[109]	Tetra(phenylethynyl)tin	140	0.25	-	599.9	1.91	Buk
L-Lactide[110]	[{1-Isopropyl-3-(N-phenylacetamido)imidazol-2-ylidene}+ Cl	100	4.000	-	13.5	1.23	Bulk
D,L-Lactide[111]	$[(Me_3\ TAC)_2\ Pr(OTf)_3]$	170	18.00	-	1.8 M|	-	Bulk
D,L-Lactide[112]	$[(Me_3SiNCH_2CH_2)_2NMe]AlH$	80	160.0	-	16.93	1.72	Ben
D,L-Lactide[112]	$\{[(Me_3SiNHCH_2CH_2)(Me_3SiNCH_2CH_2)NMe]AlCl\}\{AlCl_4\}$/PO	80	600.0	-	18.50	1.39	Ben
D,L-Lactide[113]	$(CH_3\ COO)_3\ La$	140	24.00	-	54.8 M|	-	Bulk
D,L-Lactide[113]	(CCl3COO)3 Y	160	30.00	-	59 M|	-	Bulk
D,L-Lactide[113]	(CCl3COO)3 La	160	1.000	-	72 M|	-	Bulk
D,L-Lactide[113]	(CCl3COO)3 Sm	160	10.00	-	69 M|	-	Bulk
D,L-Lactide[113]	(CCl3COO)3 Nd	160	11.00	-	71 M|	-	Bulk
L-Lactide[114]	Mg/BnOH	83	2.000	-	45.2	1.21	$C_2H_4Cl_2$
D,L-Lactide[115]	$Sn(O\textit{i}\ Pr)_4$	70	8.500	-	36.7	1.29	Tol
D,L-Lactide[115]	$Sn(Oct)_2$	70	8.000	-	34.2	1.05	Tol
D,L-Lactide[115]	$Sn(O\textit{t}Am)_4$	70	8.500	-	43.6	1.47	Tol
rac-lactide[116]	Sn–*rac*-LA	80	2.000	-	30.8	1.2	Tol
rac-lactide[116]	Sn–CL	130	2.000	-	430.1	1.3	Bulk
L-Lactide[117]	$[(SalenMe)Mg(OBn)]_2$	25	0.750	-	27.3	1.09	Tol
L-Lactide[117]	$[(SalenMe)Zn(OBn)]_2$	25	4.500	-	34.1	1.03	Tol
D,L-Lactide[118]	$[(L^{Me2})(HL^{Me2})Y_3(OCH_2C_6H_5)_4]$	25	16.00	-	14.5	1.23	CH_2CL_2
L-Lactide[119]	$Ti(OPr\ \textit{i}\ )_4$	130	2.000	-	10.54	1.90	Tol
L-Lactide[120]	Bu_2SnOct_2	120	24.00	-	0.52	-	Bulk
L-Lactide[121]	Red-Al	110	48.00	-	23	1.12	Tol
rac-Lactide[122]	$(MeMgOEt_2)$bamam-1	RT	2.500	-	61.1	1.44	$CDCL_3$
L-Lactide[123]	Iron Isobutyrate	190	2.000	-	148	1.60	Bulk
L-Lactide[124]	Strontium Isopropoxide	80	3.000	0.789	45.4	2.26	Tol
L,L-Lactide[125]	$Sn(Oct)_2$	110	50.00	-	304	2.25	Bulk

Contd.

L-Lactide[126]	$La(OTBP)_3$	100	0.333	-	46.9	1.49	Tol
D,L-lactide[127]	$K[CuL]2H_2O$	130	24.00		$4.86^{M\eta}$	-	Bulk
D,L-lactide[127]	$K[ZnL]2H_2O$	130	24.00		$5.23^{M\eta}$	-	Bulk
D,L-lactide[127]	$K[CoL]3H_2O$	130	24.00		$5.26^{M\eta}$	-	Bulk
D,L-lactide[127]	$K[NiL]3.5H_2O$	130	24.00		$11.1^{M\eta}$	-	Bulk
rac-Lactide[128]	[(R)-(SalBinap)AlOiPr] [(R)-1]	70	40.00	-	22.6	1.09	Tol
L- L actide[129]	Zn pyroglutamate	150	48.00	0.53	-	-	Bulk
L- Lactide[129]	Zn tosglycinate	150	96.00	0.52	-	-	Bulk
L-Lactide[130]	$(BDI\text{-}OMe)Zn(\mu\text{-}OBn)\}_2Zn(\mu\text{-}OBn)_2$	25	0.166	-	29	1.06	Bulk

$M\eta$ -Viscosity average molecular weight, Tol-Toluene, THF-tetrahydrofluorine, DCM-Dichloromethane, Ben-Benzene, CE-Crown ethers, CB- Chlorobenzene, PO-Propylene oxide, Gl-glycolide, La- lactide, Cap- ε-caprolactone, PDI-Polydisperity index



Scheme 3 — Cationic polymerization mechanism

Microwave assisted ROP (MROP) with organo metallic catalyst is an appealing route for ring opening due to its high efficiency and uniform heat distribution during the reaction. ROP and polycondensation reactions are very impressively accelerated by microwave irradiation[74,75]. Zhang *et al*[76] achieved molecular mass of 10^5 g/mol using D,L-lactide with microwave energy (255W) for 10 min. However, higher microwave energy with increasing time causes chain scission and reduces molecular mass to oilgomers and cyclic dimers. Li *et al*[77] observed that MROP shows higher rate of conversion and high molecular mass product compared with conventional ROP.

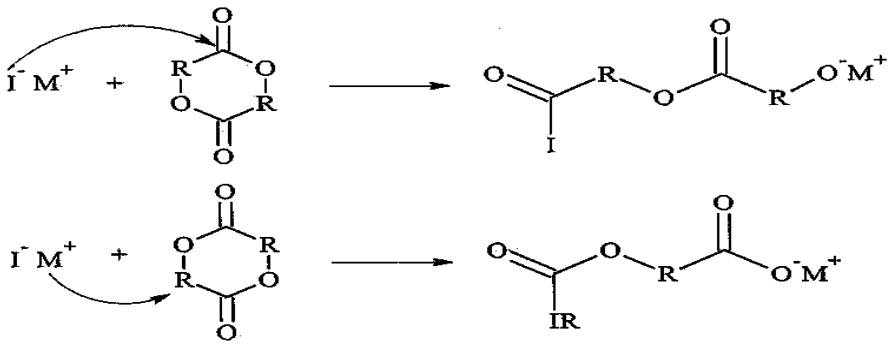
Pure D and L forms of lactic acid monomer produce isotactic polylactic acid. Syndiotactic polylactic acid was produced by *meso*-lactide. Polymerization occurs without any stereoregularity led to heterotactic polylactide. Rate of bio-absorption or degradation rate, mechanical and thermal properties depends on microstructural arrangement of polymers[78]. Recently, many researchers have carried out ROP of lactide and other bio-absorbable polymers (Table 2).

Cationic Polymerization

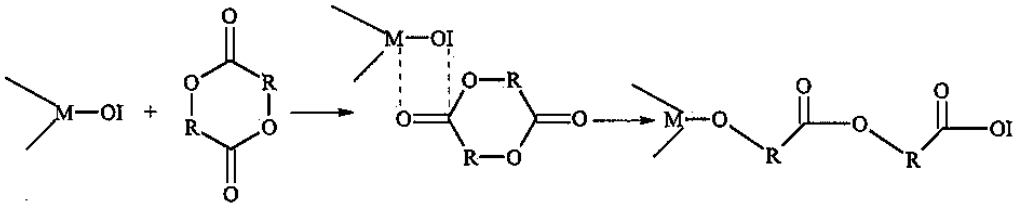
Cationic ROP involves extremely strong acids or carbenium ion donors, which are capable of initiating a cationic polymerization of cyclic dimers. Formation of positively charged species and subsequent attack by monomer results in ring opening of positively charged species[130,131] (Scheme 3). Kricheldorf *et al*[132] reported that cationic polymerization is difficult to control at higher temperature, which tends to more or less racemization and this affect properties of polymers rather slowly under 50°C. Among numerous acidic compounds investigated, only trifluoromethane sulfonic acid (HOTf) and methyl trifluoromethane sulfonate (MeOTf) proved to be efficient initiators. Polymerization rates were significantly higher in nitrobenzene than in chlorinated solvents, and 50°C being optimum reaction temperature. But, lower temperatures result in modest yields and higher temperatures lead to dark-coloured samples. Optical rotation measurements revealed that samples of 100% optically active poly(L-lactide) are obtained from L-lactide using HOTf and MeOTf[133, 134].

Anionic Polymerization

Under anionic polymerization, nucleophilic attack of a negatively charged initiator on carbonyl group or on carbon atom adjacent to acyl-oxygen results in ring opened linear polyester (Scheme 4). Lactide ions can initiate a new chain and thereby deprotonation of monomer leads to chain transfer process. Kricheldorf



Scheme 4 — Anionic polymerization mechanism



Scheme 5 — Coordination insertion mechanism

et al[135] proposed bulk polymerization of lactide using $FeLac_2$ at 150°C and observed that $FeLac_2$ caused intensive racemization of monomers. But, ZnI_2 yield a moderate molar mass (optical purity, 97%) even at 120-150°C[136]. Ionic chain ends in anionic and cationic polymerisation of lactones causes transesterification reactions even at moderate temperatures and results in cyclization. Imidazole and *N*-methylimidazole catalyzed lactide polymerization gave low molar mass cyclic polymer at 100°C[137].

Coordination Insertion ROP

Coordination insertion ROP mechanism enhances electrophilicity of CO-group and nucleophilicity of OR-groups so that an "insertion" of lactone into metal O-bond may occur[138] (Scheme 5). Propagating chain remains attached to metal through an alkoxide bond during propagation. Reaction is terminated by hydrolysis forming a hydroxyl end-group. Macromers with active end-groups are produced in post polymerization reactions of functional alkoxy substituted initiators[139].

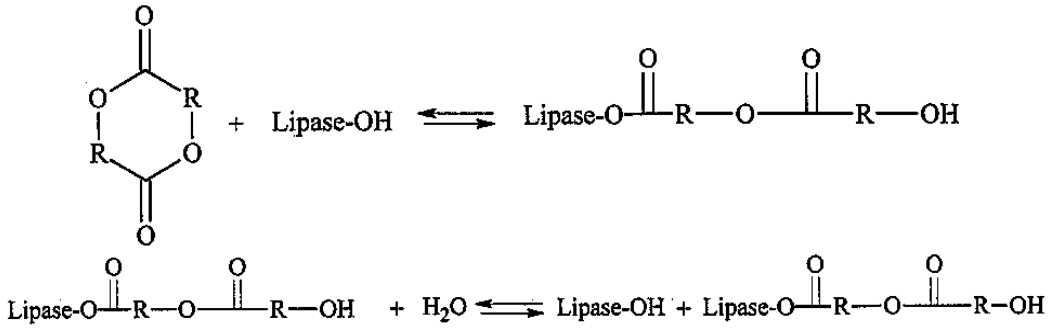
Enzymatic Ring Opening Polymerization

Enzymatic polymerization can be carried out using low temperature by enzyme activated monomers (EAM)[140,141]. Lipase catalyzed polymerization is an eco-friendly technique for preparation of useful polyesters by polycondensation as well as ring opening polymerization (Scheme 6). Enzyme-catalyzed reactions accelerate chain degradation and backbiting at high temperatures[142,143].

Properties of Bio-absorbable Polymers

Thermal Properties

Glass transition temperature (Tg) of important BAP's is as follows: PLA, 55-60; PGA, 35; and PDO, -10°C. Melting temperature (Tm) is as follows: PLA, 145-180° and PGA, 220-230°C. After molding, internal stress tends to generate micro cracks, affecting overall performance of polymer[144-146]. Internal stress can be removed by annealing material for 4 h at 120°C after molding. Lamellar crystallites in poly(L-lactide) appears to be very stable towards hydrolysis[147]. Generally, PLA exhibits left-handed helix conformation for a-form. Fibers can be drawn in the case of high molar mass PLLA, which can change to stable b-form[148-150]. PGA has better thermal stability than PLA. Thermal degradation of PLA and PGA in random chain scission shows activation energies of 16.5 and 10.2 kcal/mol and in specific chain end scission, it absorbed 28 and 22.2



Scheme 6 — Enzymatic ring opening polymerization

kcal mol respectively[151]. Thermal degradation is very fast in presence of moisture because PLA, PGA and PDO are moisture and heat sensitive. Degradation that occurs under hydrolysis in presence of a trace amount of water, zipper-like depolymerization due to shearing on processing, random main chain scission by oxidation and intermolecular transesterification results in low molar mass product[152,153].

Mechanical Properties

PLA, PGA and PDO exhibit good mechanical properties among all synthetic BAP's. PGA and PLA have tensile strength usually 40-140 MPa. Elastic modulus is a follows: PLA, 2.7; PGA, 7.0; and PDO, 1.5 GPa. PGA shows higher elongation and tensile modulus than PLA[154-158]. These values are lower than those of cortical bone[159,160], which has: bending strength, 180-195 MPa; shear strength, 68 MPa; and elastic modulus, 6-20 GPa. Good mechanical strength of BAP is attainable if material is self-reinforced (SR) by sintering[161,162]. SR polymeric composites significantly increase strength, ductility and elastic modulus. Composite structure of SR polymer made up of polymeric material comprised of oriented reinforcing units and a binding matrix. Both matrix and reinforcing materials are in crystalline nature and high degree of similar molecular orientation makes SR polymer implants to be stiff and strong in oriented direction[154]. For SR-PLLA pins, an initial bending strength of 300 MPa and shear strength of 220 MPa needed[161]. For SR copolymers, bending strength and Initial shear strength values, respectively, are as follows: SR-Poly(L-DL)LA (70:30), 214 MPa[162] , 121 MPa[162]; and SR-PLA/PGA (80:20), 226 MPa[163], 115 MPa[150]. Elastic modulus of SR pins is 6-10 GPa[154,161-163] being close to that of cortical bone. New fabrication technologies have been developed to process BAPs into tissue engineering scaffolds[164-166].

Bio-absorbable Properties

Biodegradation[151-154] mainly depends on type of material, molar mass, percentage of crystallinity, type of environment (enzymatic concentration, external stress) and material molding history (internal stress). BAP has been accomplished with hydrolytically unstable linkages in backbone, which tend to lose molar mass after implantation. Material undergoes specific and/or non-specific degradation *in vivo*[155-157]. PLA and PGA produces acid product during degradation. PDO has manifested into nontoxic material on decomposition. Toxic effect can occur when chemical or enzymatic catalyst or buffering agent is used[151,157,158]. Continuous scission causes higher rate of monomer conversion. In thick and bulky implants, degradation is disorderly between surface and core portion due to surrounding tissue. Adhesion of tissue on surface results in high rate of degradation. Fine surface and/or less porosity have a better tendency to withstand acid break down and reduce hydrolysis[159-161]. Molecular construction (R-group), degree of crystallinity and micro structure intervene in degradation rate. Amorphous region retains higher amount of water due to high free volume and more segmental mobility, thereby leading to fast hydrolytic degradation compared to crystalline region. Crystalline region can act as a reinforcement, which increases degradation time and mechanical properties[162-166].

Self-reinforced homopolymer of PLA shows higher strength and high crystallinity. It takes over five years for complete absorption and amorphous poly (D, L-Lactide) can absorb in 1.5 years[167,168]. Copolymer of PGA-PLA shows faster degradation than homopolymer of PLA. PDO and PGA degrade around two months and complete reduction of molar mass occurs in 9-12 months[169]. R-group of PGA is more sensitive towards water. By varying composition of PLA and PGA, degradation rate can be specified without rapid

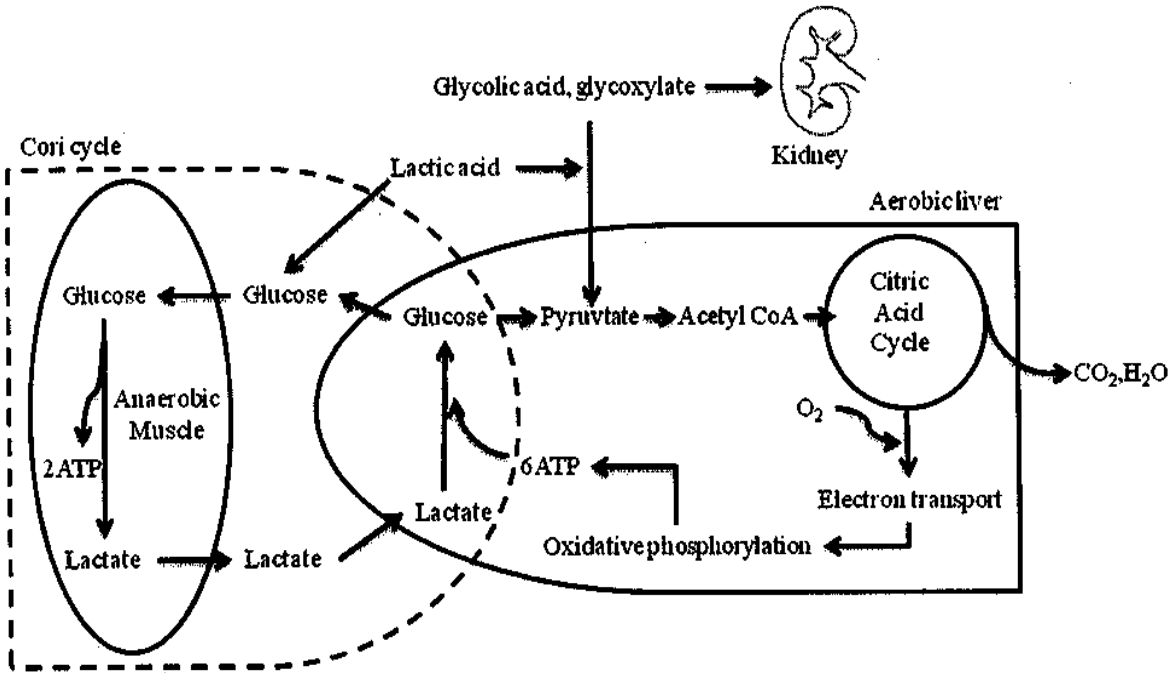


Fig. 1— Bio-absorption of monomers in metabolism

degradation and control release of acidic breakdown products. Hydrolysis of PLA, PGA and PDO breaks down into lactic acid, glycolic acid and glycoxylate respectively. Glycolic acid and glycoxylate are excreted via kidney or converted as pyuvate and further conversion into acetyl CoA involving citric acid cycle. Lactic acid can be converted into glucose, which further breaks down into adenosine triphosphate (ATP) via cori cycle (energy cycle) (Fig. 1)[170-172].

Applications

Many polymer devices commercially available are most commonly smart screws, smart pins (SR-LPLA-Bionx Implants), phantom softhread soft tissue fixation screw (LPLA-DePuy), orthosorb pin (PDO-J and J Orthopedics), biologically quiet staple (85:15/DL-PLGA-Instrument Makar), meniscal stinger (LPLA-Linvatec) and bio-anchor (LPLA-Linvatec). Denti *et al*[173] investigated effect of four different bioabsorbable interference screws for bone block fixation. PLLA screw (Linvatec), PGA screw (Smith & Nephew), PLA-co-PGA screw (Instrument Makar), PLA screw (Arthrex) are available commercially and reported that PGA screws are absorbed more quickly than PLA.

Orthopaedic Application

Bio-absorbable implants in orthopaedic surgery have mainly been used to eliminate implant removal operations[174-176]. Self reinforced PLA and PGA screws and rods have excellent strength for bone fixation. PLA (molar mass, 1,00,000) has excellent mechanical property for implantation and other applications. PGA (molar mass, 20,000-1,45,000) is used for orthopaedic implants[177,178]. To a large extent with orthopaedic and traumatologic implants involved, incidence of infection[179] in conjunction with bio-absorbable osteosynthesis devices ranges from 3-4%. To facilitate tissue regeneration and uniform load transformation, scaffolds are used as a temporary support to body structures. Reconstruction of finger joints was performed using scaffolds folded of VicrylR (co-polymer of 90% PGA and 10% PLLA) or EthisorbR (made up of PDS and co-polymer of 90% PGA and 10% PLLA) fleeces[180]. Recently, electrospun nanofibrer scaffolds showed greater promise and potential for many biomedical applications [tissue engineering, wound dressing, immobilized enzymes and controlled-delivery of drugs (genes)].

Tissue Engineering

In tissue engineering, PDO scaffolds performed with high flexibility, slow degradation, higher strength retention and lower inflammatory response rates when compared to Vicryl (glycolic-co-lactic acid polymer) and Dexon (polyglycolic acid). Monofilament suture typically looses 50% of its initial breaking strength after 3 weeks[181,182]. Degradation time of PLA-PGA scaffolds depends upon the ratio of monomers in copolymer composition. Optimum pores for bone regeneration, regeneration of skin and in growth of cells are 100-150, 20-125 and 20-60 respectively[183]. Surface modification of electrospun scaffolds with suitable bioactive molecules can effectively increase biological activity, useful for specific biomedical applications[184]. Polyheterocycle based nanoparticles–PLA composites are observed as a biocompatible conducting material, which can be used as a biosensor for tissue engineering[185,186]. *In vivo* study suggested that polyheterocycles would have slow degradation and renal clearance[187,188].

Control Drug Delivery Systems

Control drug release can occur by desorption of surface bound drug and/or diffusion through nanoparticle matrix. Biodegradable materials are intended to degrade within the body after release of active agent has been completed. This eliminates need for removal of material after drug release[189-193]. BAP's can be tailor-made to achieve both controlled drug release and disease specific localization by tuning polymer characteristics by varying copolymer ratio to crystallinity can control via drug delivery[194-210]. PLGA (Poly(lactic-*co*-glycolic acid)) of different molecular weights (10-100 kDa) having different copolymer ratios (50:50, 75:25 and 85:15) are available in the market. Molecular weight and copolymer molar ratios influence degradation process and release profile of the drug entrapped[211,212]. Nanoparticals with high crystallinity could lead to the formation of a microchannel structure and a large surface area in polymer matrix, making drug release easily[213].

Storage and Sterilization

Implanting bio-absorbable device should be sterilized by g-radiation or ethylene oxide (EtO) or plasma etching before clinical use[212-214]. Molecular weight, mechanical property and performance of polymers are also dependent on sterilization and storage conditions. EtO sterilization residual gas causes toxic effect in body and hence not a preferable method for bio-implants[215]. g-radiation is preferable method for bio-implants; low dose of 250 kGy g-radiation enhances chain scission in polymer and higher dose introduce crosslink's between linear chains[216-218]. Bio-absorbable materials are stored in low temperature, dry environment and low humidity[219].

Conclusions

Use of BAP's has marvelous growth in a variety of biomedical applications. Polymer implantation devices are convenient to design structure and tailor-made property according to environment and usage conditions. Replacements of heavy metal implants by BAPs have been successively carried out. For material development, non-toxic catalyst with simple polymerization method needed. For optimum performance, BAP's should be sterilized and preserved under ideal conditions.

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