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BIODEGRADABLE POLY(LACTIC ACID) AND POLY (LACTIDE-CO-GLYCOLIDE) POLYMERS IN SUSTAINED DRUG DELIVERY:

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ABSTRACT:

Poly(lactic acid) [PLA] and its co-polymers with glycolic acid [PLCG] have been known for the past 20 years of its biodegradability and histocompatibility. Their physico-chemical and biological properties have been found suitable, in many instances, for sustaining drug release in vivo and in vitro from days to months. A wide variety of drugs ranging from small molecular weight therapeutic agents to peptide hormones, antibiotics, chemotherapeutic drugs have been studied using these biodegradable polymers. Several parenteral and oral dosage forms have been investigated, which includes microcapsules, implants, pseudolatices, nanoparticles, tablets, films as well as occular devices for local delivery of drug into the eye. An attempt have been taken in this paper to review the prospect of using these biodegradable polymers for long term parenteral drug delivery of different classes of drugs.

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INTRODUCTION:

Many oral sustained release products have been successfully formulated and exist in the drug market, but these products are usually unsuitable for delivering a drug for more than 24 hours. Moreover, peptide drugs and drugs which are unstable in the GI tract can't be delivered by oral route and require parenteral administration. Long term parenteral dosageforms are difficult to formulate particularly for the drugs of very short half life, hormones and peptide drugs. Benzathine penicillin, medroxy progesterone acetate, zinc insulin etc. are typical examples of long term parenteral delivery systems; but they are chemically modified or physical conjugates of the active drug and only applicable to some specific drugs. However, fabricating drugs in a polymeric device may be non-specific where un-modified drug could be released either by diffusion through the polymer barrier or by erosion of the polymer matrix. A wide range of polymers have been synthesized for this purpose. Examples of early polymeric devices for parenteral administration were prepared from silicon rubber[1] and polyethylene[2]. A serious drawback to using these inert polymers as parenteral implants is their non-biodegradability, which require surgical removal of the implants after drug exhaustion. These non- biodegradable polymers may also cause toxicological problems[3]. To overcome these problems, the concept of biodegradable polymers for sustained release parenteral drug delivery began to be developed in the early 1970's.

Biodegradable polymers may be defined as synthetic or natural polymers which is degradable in vivo either enzymatically or non-enzymatically to produce bio-compatible or non-toxic by-products. These can be further metabolized or excreted via normal physiologic pathways.

Natural biodegradable polymers include Human Serum albumin, Bovine serum albumin, Gelatine, Collagen, Haemoglobin etc. and their use may be limited by the large scale commercial manufacturing and difficulties in purification. Whilst synthetic bio-degradable polymers may be obtained in relatively cheaper cost. Aliphatic polyesters, poly(alkyl-α-cyano acrylates), poly (amides), poly (amino acid), poly (orthoesters), poly (urethanes), poly (acrylamides) etc. are probable candidates for synthetic biodegradable drug carriers. Amongst these aliphatic polyesters, such as, poly(lactic acid) [PLA], poly(glycolic acid) [PGA] and poly(lactide-co-glycolide) [PLCG] have been attracted most because of their good histo-compatibility and bio-degradability. Bio-degradation and and tissue reactions of PLA and PLCG polymers have been investigated extensively by many workers[4-10]. In this paper the release properties of different classes biologically active compounds from PLA and PLCG matrix systems are discussed.

USE OF PLA & PLCG IN DRUG DELIVERY:

Yolles et al[11] first reported the use of PLA in parenteral drug delivery. Since then a wide range of drugs have been investigated using PLA and its co-polymers with glycolic acid to form microcapsules[12-16], microparticles[17,18], implants[19-22], pseudolatices[23], nanoparticles[24], as well as occular devices for local delivery of drug into the eye[25,26]. The development of injectable controlled release microcapsules for contraceptive steroids and other potent drugs has now progressed to the stage of human trial[27]. Microcapsules are of particular interest, because it is possible to make spherical particles of less than 100 μm suitable for injection using a hypodermic needle. These biodegradable polymers may release the active compound by either diffusion or erosion of the matrix or both.

NARCOTIC ANTAGONISTS:

The initial use of PLA as a long acting drug delivery was for narcotic antagonists[11]. Schwope et al[28] found that the rate of naltrexone release from PLCG polymeric implants were dependent on the lactide(L) and glycolide(G) ratio in the co-polymer, which was of the following order, 75L/25G > 100L > 90L/10G. These implants also followed a dose dependent zero order release kinetics. They also reported a higher release rate of naltrexone when compared with naltrexone palmoate. The latter was less soluble in water than naltrexone. The additional coating of pure polymer surrounding the matrix prolonged the duration of release. Naltrexone palmoate microencapsulated using a DL-PLA polymer was reported by Harrigan et al[29]. They found 42 to 51 days of therapeutic activity in monkey following an injection of microcapsules of < 160 μm size suspended in peanut oil.

Woodland et al[30] used cyclazocin in the form of implants and microparticles prepared by grinding a melt cooled mixture of the polymer and the drug. Two molecular weights (45,000 & 70,000) of the DL-PLA were used. They showed that the release rates were insensitive to the variations in the polymer molecular weights. In their experiments with implanted films the release rate of cyclazocin in vivo was faster than in vitro, whilst the effect was opposite with microparticles. They explained this release behaviour by the fact that, films caused inflammation and the accumulation of body fluid at the implant site, thereby increased release rate compared to small articles, which did not cause such inflammation. Increased temperature and variation in chemical composition of the body fluids surrounding the implanted film could have some effect on the release rate.

CONTRACEPTIVE STEROIDS:

Biodegradable polymers have been effectively used to alter the kinetics, bioavailability, duration of action and method of administration of contraceptive steroids[31]. Several natural and synthetic contraceptive steroids such as progesterone, norethisterone norgestrel, norgestimate, ethinyl-estradiol etc. have been microencapsulated using PLA and PLCG polymers to produce parenteral injection with programmed duration of action ranging from one month to six month per injection[32]. DL-PLA & L-PLA injectable matrices of contraceptive steroids were also patented[17]. Jackaniez et al[18] reported both in vitro and in vivo release of norgestrel for 80 days from PLA films.

Extensive studies were done using several contraceptive steroid in the form of microcapsules using PLA and PLCG[33-36]. Their studies showed that these microcapsules were capable of sustaining steroid release for 3 to 6 months in vitro and in vivo in rats and baboon. They showed that the duration of such system depended on the molecular weight of polymers and molar composition of lactide/glycolide ratios in the co-polymer, PLCG. Their clinical studies, in woman, with these microencapsulated contraceptive steroids also showed long term steroid release without complications and adverse effects[37-38]. These workers subsequently received a patent for microcapsules containing contraceptive steroid[39].

Mason et al[40] reported intracervical injection of DL-PLA microcapsules containing 54% of progesterone. Their in vitro release studies in blood plasma showed an initial burst effect followed by a very slow release of 65 mg/day for 4 months from a dose of 200 mg of microcapsules. They did not find any significant change of microcapsule surface even after 5 months contact with plasma. Wise et al[41] studied long-term levonorgestrel release in

rats from implants of co-polymers containing 90:10 and 50:50 lactide:glycolide ratios. They reported an initial burst effect of hormone release followed by a zero order release from 90:10 PLCG. Recently Eenink et al[43] prepared hollow fibres from L-PLA polymers and filled them with 25% levonorgestrel suspension in castor oil. They reported a zero-order release in vitro from these reservoir devices. In vivo experiments in rabbits exhibited a constant blood levels for 210 days.

OTHER STEROIDS:

Several steroids, other than contraceptive steroids have also been incorporated in PLA and PLCG matrix system as both implants and microcapsules. Smith and Hunneyball[55] studied the release of prednisolone from microspheres and microparticles, as well as from compressed implants of these. They showed a rapid release of drug both in vivo and in vitro from small particles compared to those of implants. Yolles & Sartori[56] reported in vivo dexamethasone release in dogs from PLA polymer "chips" and "composites" containing 10% of the drug. They found an initial burst effect followed by a sustained release of drug for 60 days. Another anti-inflammatory steroid, triamcinolone acetonide has been incorporated in PLA matrix as colloidal nanoparticles (< 1 μm) which accumulated predominantly in liver, kidney and bone marrow, following an intravenous injection[24]. Gurny et al[23] prepared a pseudolatex, suitable for injection containing testosterone. They also reported testosterone release from artificial testes prepared from both bio-degradable and non-degradable polymers. The duration of release from non-biodegradable vinyl polymers was longer compared to that of biodegradable PLA polymer, because the latter is degraded in vivo releasing the content rapidly.

LH-RH ANALOGUE:

Leutinizing hormone releasing hormone (LH-RH) analogues are short chain peptide hormones with a very short half life of 30 minutes to 3 hours. They have been successfully encapsulated using PLCG polymers[44-48]. Encapsulation protects the hormone from proteolytic degradation and controls the release rate. The bioavailability of LH-RH can be increased up to 30,000 times to that of the same analogue administered in non-encapsulated form[32]. There are also reports on the long term delivery of these peptides from implants prepared from of PLCG polymers[49]. Leuprolide, a LH-RH analogue for prostate cancer therapy has been studied by Kaetsu et al[50] in the form of implantable needles. These peptide hormones are not soluble in the polymer membrane and cannot release by simple diffusional mechanism, as a result the release mechanism is dependent on the polymer degradation and erosion of the matrix itself. Extensive release studies of Leuprolide acetate, a LH-RH analogue, has been carried out both in vivo and in vitro by Ogawa and co-workers[51-54]. Their results clearly demonstrated the effect of PLA and PLCG polymer molecular weight on the duration of peptide release. This degradation and erosion rate is highly dependent on both polymer molecular weight and molar ratio of lactide and glycolide components in the PLCG co-polymer chain.

CHEMOTHERAPEUTIC AGENTS:

Doxorubicin had been encapsulated using PLA polymers by Juni et al[57] and showed a sustained release of the drug compared to the pure non-encapsulated drug, following intra-arterial injection into the dog. They also showed that the microspheres were capable of embolizing peripheral blood vessels of the liver. Tsai et al[58]

microencapsulated mitomycin-c using a PLA polymer and found dose dependent sustained antiproliferative activity against the growth of K562 human erythroleukamia cells. Yolles & Morton[59] reported in vitro release of cis-dichlorodiamine platinum alone and in combination with cyclophosphamide and doxorubicin from PLA microparticles and tested in vivo against Ascites Sarcoma 180 in mice. They reported a prolonged life span of the experimental rats compared to the controls, following intraperitoneal injection of microparticles. There also a report on the cisplatin loaded DL-PLA microspheres for chemoembolization[60]. Microencapsulated 5-FU using DL-PLA has been shown to reduce X2 tumor in rabbits more efficiently than intra-arterial infusion of non-encapsulated 5-Fluoro Uracil (5-FU)[61]. The same group of workers also found release of 5-FU from PLA implants for 30 days and remarkable inhibition of growth of AH130 Ascites Hepatoma implanted intra-dermal in rats[62].

LOCAL ANAESTHETICS:

Wakiyama et al[63] reported the preparation of butamben, dibucain and tetracain microspheres using a DL-PLA polymer. The in vivo effectiveness of dibucain microspheres was investigated in guinea pigs and found local anaesthetic effect of 300 to 400 hours depending on dose. This effect lasted for only 90 minutes with non-encapsulated dibucain HCl. However, the release profile of dibucain microspheres in vivo was different than those from in vitro because of difference in the bio-degradation rates[64]. These workers also showed that both in vivo and in vitro release rate is dependent on the core solubility in the bulk phase. The degradation rate of the poly(lactic acid) microspheres also reported to be affected by the presence of basic core, Tetracain[65].

ANTIBIOTICS:

Vidmar et al[66] reported oxytetracycline microcapsules of two different molecular weights of DL-PLA. Microcapsules prepared from a high molecular weight (38,000) polymer released slowly compared to those of low molecular weight (20,000) polymer. The drug was released totally from the high molecular weight polymer within 12 hours *in vitro* and took 24 hours *in vivo* in rabbits. Whilst there was no appreciable difference in plasma profile with low molecular weight polymer microcapsules and the non-encapsulated oxytetracycline *in vivo*, possibly because of the higher degradation rate of the low molecular weight polymer. Their *in vitro* release showed a square root of time dependent release. Setterstorm et al[67] reported microencapsulation of ampicillin for wound infection using a PLCG co-polymer. Their microcapsules showed dose dependent release for 2 weeks when injected subcutaneously in rats. Application of ampicillin microcapsules after artificially induced infection in rats showed better efficacy than the non-encapsulated ampicillin.

ANTIMALARIALS:

Wise et al[21] used 2,4-diamino-6-(2-napthyl sulphonyl)-quinazoline (WR-158122), an anti malarial agent to prepare microparticles with 25:75 PLCG. Their *in vivo* experiments showed that some mice survived for 14 weeks injected with drug-polymer beads. Whilst all mice in the control group become malarious and survived only an average of 12 days following injection. Wise et al[68] also reported efficacy of sulphadiazine against *Plamodium berghei* from matrix beads of 1.5 mm diameter. They found that the co-polymer of L-PLA and DL-PLA (90:10) was most efficient and released the drug for 3 months. A dual antimalarial system, containing sulphadiazine and WR-158122 was made with 90:10 PLCG

co-polymer as matrix type microparticles[69]. The authors reported long term release of both drugs. However, they stated that the release of sulphadiazine was faster than desired.

CONCLUSION:

Besides above mentioned pharmcologic groups of drugs, some other biologically active compounds have also been investigated using these PLA or PLCG polymers. But the greatest interest remains with the delivery of peptide drugs, because they usually have very short half life and can not be administered by oral route. The recent advancement of biotechnology and genetic engineering may produce new biologically active peptides. A long term delivery of such products will require a biodegradable polymer and poly(lactic acid) and its co-polymers stands a very good chance in that respect.

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