REVIEW ARTICLE Am. J. PharmTech Res. 2013; 3(6) ISSN: 2249-3387

AMERICAN JOURNAL OF PHARMTECH RESEARCH

Journal home page: http://www.ajptr.com/

Biodegradable Polymeric Nanoparticles For Drug Delivery And Targeting

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ABSTRACT

This review presents the numerous researches which explore the potential use of polymeric nanoparticles as carriers for a wide range of drugs for therapeutic applications. Because of their versatility and wide range of properties such as better encapsulation, control release and less toxic properties, biodegradable polymeric nanoparticles are being used as novel drug delivery systems. In particular, this class of carrier holds tremendous promise in the areas of targeted drug delivery system.

Keywords: Nanoparticles, biodegradable polymer

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Received 22 November 2013, Accepted 28 November 2013

Please cite this article in press as: Mehare G. *et al.*, Biodegradable Polymeric Nanoparticles For Drug Delivery And Targeting. American Journal of PharmTech Research 2013.

INTRODUCTION

Over the past few decades, there has been considerable interest in developing biodegradable nanoparticles (NPs) as effective drug delivery devices. Various polymers have been used in drug delivery research as they can effectively deliver the drug to a target site and thus increase the therapeutic benefit, while minimizing side effects[1.] The controlled release (CR) of pharmacologically active agents to the specific site of action at the therapeucally optimal rate and dose regimen has been a major goal in designing such devices. Liposomes been used as potential drug carriers instead of conventional dosage forms because of their unique advantages which include ability to protect drugs from degradation, target the drug to the site of action and reduce the toxicity or side effects[2]. However, developmental work on liposomes has been limited due to inherent problems such as low encapsulation efficiency, rapid leakage of water-soluble drug in the presence of blood components and poor storage stability. On the other hand, polymeric NPs offer some specific advantages over liposomes. For instance, NPs help to increase the stability of drugs /proteins and possess useful CR properties.

Nanoparticles generally vary in size from 10 to 1000 nm. The drug is dissolved, entrapped, encapsulated or attached to a NP matrix and depending upon the method of preparation, nanoparticles, nanopheres or nanocapsules can be obtained. Nanocapsules are vesicular systems in which the drug is confined to a cavity surrounded by a unique polymer membrane, while nanospheres are matrix systems in which the drug is physically and uniformly dispersed. In recent years, biodegradable polymeric NPs have attracted considerable attention as potential drug delivery devices in view of their applications in the CR of drugs, their ability to target particular organs / tissues, as carriers of DNA in gene therapy, and in their ability to deliver proteins, peptides and genes through a peroral route of administration [3,4]

Synthesis and characterization

As stated previously, there are several different methods for preparing nanoparticles. Additionally, numerous methods exist for incorporating drugs into the particles. For example, drugs can be entrapped in the polymer matrix, encapsulated in a nanoparticle core, surrounded by a shell- like polymer membrane, chemically conjugated to the polymer, or bound to the particle’s surface by adsorption. A summary of these methods including the types of polymer, solvent, stabilizer and drugs used is given in Tables 1.

Table 1: Summary Methods used for preparation of Polymeric Nanoparticles

Method	Polymer	Solvent	Stabilizer	Size (nm)	Ref.
Solvent diffusion	PLGA	Acetone	Pluronic F-27	200	33
	PLGA	Acetone/DCM	PVA	200 - 300	19
	PLGA	Popylene Carbonate	PVA/PVP	~100	16
Solvent Displacement	SB-PVA-g-PLGA	Acetone/Ethyl Acetate	Poloxamer 188	~ 100	32
Nanoprecipitation	PLGA/PLA/PCL	Acetone	Pluronic F68	110-208	20
	PLGA	Acetonitrile	-	157.1±1.9	18
Solvent Evaporation	PLGA	DCM	PVA	800	10
	PEO-PLGA	MC	PVA	150±25	8
Multiple Emulsion	PLGA	Ethyl Acetate/MC	PVA	335-743	34
	PLGA	DCM	PVA	213.8±10.9	14
	PLGA	DCM/Acetone	PVA	100	9
	PLGA	DCM	PVA	~ 250	6
	PLGA	Ethyl Acetate	PVA	192 ± 12	12
	PLGA	Ethyl Acetate	PVA	~ 300	7
	PLGA	DCM	PVA	380 ± 40 - 1720 ± 110	13
Salting Out	PLA	Acetone	PVA	300–700	21
Phase Inversion Nanoprecipitation	PLGA	MC	–	>5 mm	15
Polymerization	CS-PAA	–	–	206 ± 22	25
	PECA	–	Pluronic F68	320 ± 12	31, 26
	PE-2-CA	–	–	380 ± 120	30

The most common method used for the preparation of solid, polymeric nanoparticles is the emulsification solvent evaporation technique. This technique has been successful for encapsulating hydrophobic drugs, but has had poor results incorporating bioactive agents of hydrophilic nature. Briefly, solvent evaporation is carried out by dissolving the polymer and the compound in an organic solvent. Frequently, dichloromethane or methylene chloride is used for PLGA copolymers. The emulsion is prepared by adding water and a surfactant to the polymer solution. In many cases, the nano sized polymer droplets are induced by sonication or homogenization. The organic solvent is then evaporated and the nanoparticles are usually collected by centrifugation and lyophilization [5, 8–11].

A modification on this procedure has led to the protocol favored for encapsulating hydrophilic compounds and proteins, the double or multiple emulsion technique. First, a hydrophilic drug and a stabilizer are dissolved in water. The primary emulsion is prepared by dispersing the aqueous phase into an organic solvent containing a dissolved polymer. This is then reemulsified in an outer aqueous phase also containing stabilizer [6,7,9,12–14]. From here, the procedure for obtaining the nanoparticles is similar to the single emulsion technique for solvent removal. The main problem with trying to encapsulate a hydrophilic molecule like a protein or peptide-drug is the rapid diffusion of the molecule into the outer aqueous phase during the emulsification. This can result in poor encapsulation efficiency, i.e. drug loading. Therefore, it is critical to have an immediate deposit of a polymer membrane during the first water-in-oil emulsion. Song et al. [9] was able to accomplish this by dissolving a high concentration of high molecular weight PLGA into a the oil phase consisting of 80:20% weight dichloromethane / acetone solution. Additionally, the viscosity of the inner aqueous phase was increased by increasing the concentration of stabilizer, bovine serum albumin (BSA). The primary emulsion was then emulsified with Pluronic F68 resulting in drug-loaded particles of approximately 100 nm nanoparticles [9]. Another method that has been used to encapsulate insulin for oral delivery is phase inversion nanoencapsulation (PIN). Zn-insulin is dissolved in Tris–HCl and a portion of that is recrystallized by the addition of 10% ZnSO4 . The precipitate is added to a polymer solution of PLGA in methylene chloride. This mixture is emulsified. As stated previously, there are several different methods and dispersed in 1 l of petroleum ether, which results in the spontaneous formation of nanoparticles [15].

All of the previously mentioned techniques use toxic, example, chlorinated solvents that could degrade certain drugs and proteins if they come into contact during the process. Consequently, an effort has been made to develop techniques in order to increase drug stability during the A summary of these methods including the synthesis. One such technique is the emulsification–diffusion method. This method uses a partially water-soluble solvent like acetone or propylene carbonate. The polymer and bioactive compound is dissolved in the solvent and emulsified in the aqueous phase containing the stabilizer. The stabilizer prevents the aggregation of emulsion droplets by adsorbing of the surface of the droplets. Water is added to the emulsion, to allow for the diffusion of the solvent into the water. The solution is stirred leading to the nanoprecipitation of the particles. They can then be collected by centrifugation, or the solvent can be removed by dialysis [16, 17].

One problem with this technique is that water-soluble drugs tend to leak out of the polymer phase during the solvent diffusion step. To improve this process for water soluble drugs, Takeuchi et al. [17] changed the dispersing medium form an aqueous solution to a medium chain trigkyceride and added a surfactant, Span 80, to the polymer phase. The nanoparticles are collected from oily suspension by centrifugation. Several parameters can also be changed to benefit the encapsulation of hydrophilic molecules. Govender et al. [18] found that increasing the aqueous phase pH to 9.3 and incorporating pH-responsive emulsion is formed containing polymer, acetone, magnesium acetate tetrahydrate, stabilizer, and the active methacrylic acid) (PMMA-MAA), and lauric and caprylic acid increased hydrophilic drug encapsulation without effecting the particle size, morphology, or yield. Murakami et al. [19] Effectively modified the solvent diffusion technique by using two water-miscible solvents, one with more affinity for PLGA and one with more affinity for the stabilizer, PVA, such as acetone and ethanol.

Nanoparticles can also be synthesized by the nanoprecipitation method. Briefly, the polymer and drug are dissolved in acetone and added to an aqueous solution Pluronic F68. The acetone is evaporated under reduced pressure and the nanoparticles remain in the suspension resulting in particles from 110 to 208 nm [20]. The salting-out process is another method that does not use chlorinated solvents. Using this technique, a water-in-oil emulsion is formed containing polymer, acetone, magnesium acetate tetrahydrate, stabilizer, and the active compound. Subsequently water is added until the volume is sufficient to allow for diffusion of the acetone into the water, which results in the formation of nanoparticles. This suspension is purified by cross-flow filtration and lyophilization [21]. However, one disadvantage to this procedure is that it uses salts that are incompatible with many bioactive compounds.

In most published techniques, nanoparticles are synthesized from the biocompatible polymers. However, it is possible to make biodegradable nanoparticles from monomers or macromonomers by polycondensation reactions [22,23] These processes also result in sizes ranging from 200 to 300 nm. Nanoparticles can also be made from hydrophilic polysaccharides like chitosan (CS). CS-the properties of the nanoparticles. Most importantly, if the nanoparticles can be formed by the spontaneous ionic gelatin process [12,24]. CS-poly(acrylic acid) nanoparticles have also been made by polymerization of acrylic acid and the ‘dropping method’ [25]. The resulting nanoparticles have small sizes and positive surface potentials. This technique is promising as the particles can be prepared under mild conditions without using harmful organic ‘limits’, adjusting the concentration can be a means of solvents.

The production of nanoparticles has several independent solvent variables. One key parameter is type of surfactant / stabilizer to use. A wide range of synthetic and natural molecules with varying properties has been proposed to prepare nanoparticles. Feng et al. [11] has investigated the use of phospholipids as a natural emulsifier. In their study, dipalmitoyl-phosphatidylcholine (DPPC) improved flow and phagocytal properties due to a denser packing of DPPC molecules on the surface of the nanoparticles leading to a smoother surface than particles made with the synthetic polymer, poly(vinyl alcohol) (PVA). DPPC also improved the encapsulation efficiency compared to PVA using the emulsification solvent evaporation method. In a different study conducted by Kwon et al. [16] PLGA nanoparticles prepared using didodecyl dimethyl ammonium bromide (DMAB) were smaller than particles prepared with PVA [16] Lemoine et al. [6] found that the presence of PVA in the inner aqueous phase produced smaller particles than Span 40[6]. When Pluronic has been used a stabilizer, the grade used can have a distinct effect on the size of the nanoparticles. For example, particles prepared with Pluronic F68 were smaller than particles prepared with Pluronic F108 [26].

The amount of stabilizer used will also have an effect on the properties of the nanoparticles. Most importantly, if the concentration of the stabilizer is too low, aggregation of the polymer droplets will occur and little if any nanoparticles will be recovered. Alternatively, if too much of the stabilizer is used, the drug incorporation could be reduced due to interaction between the drug and stabilizer. However, when the stabilizer concentration is between the ‘limits’, adjusting the concentration can be a means of controlling nanoparticle size. For example, using the solvent evaporation technique, increasing the PVA concentration will decrease the particle size [6,9]. However, when using the emulsification diffusion method, Kwon et al. [16] found a that a PVA concentration from 2 to 4% was ideal for creating smaller nanoparticles, |100 nm in diameter.

Another factor that can affect the nanoparticles properties is the final freeze-drying process. It has been reported that additives such as saccharides are necessary for cryoprotection of the nanoparticles in the freeze-drying process [27]. These saccharides may act as a spacing matrix to prevent particles aggregation. Because of the possibility of aggregation, freeze-drying procedure can affect the ‘effective’ nanoparticle size and consequently their release behavior and accordingly the drug pharmacokinetics [28].

The polymer used to formulate the nanoparticles will size also strongly affect the structure, properties and applications of the particles. As previously stated, PLGA has been the the most common polymer used to make biodegradable nanoparticles, however, these are clearly not the optimal carrier for all drug delivery applications. For each application and drug, one must evaluate the properties of the system (drug and particle) and determine whether or not it is the optimal formulation for a given drug application. For example, poly(butyl cyanoacrylate) nanoparticles have been successful in delivering drugs to the brain [29.] Other cyanoacrylate-based nanoparticles such as polyalkylcyanoacrylate (PACA) and polyethylcyanoacrylate (PECA), have also been prepared. They are considered to be promising drug delivery systems due to their mucoadhesive properties and ability to entrap a variety of biologically active compounds. These polymers are biodegradable, biocompatible, as well as compatible with a wide range of compatible drugs [26,30]. Furthermore, these polymers have a faster degradation rate than PLGA, which in some cases may be more desirable. PECA nanoparticles have been prepared by emulsion polymerization in the presence and absence of different molecular weight poly(ethylene glycol) (PEG), using Pluronic F68 as the stabilizer [31].

Other groups have successfully prepared nanoparticles from functionalized PLGA polymers. In one study, Jung et al. [32] synthesized nanoparticles made of a branched, biodegradable polymer, poly(2-sulfobutyl-vinyl alcohol)-g-LGA [32.] The purpose of using sulfobutyl groups attachedto the hydrophilic backbone was to provide a higher affinity to proteins by electrostatic interactions favor adsorptive protein loading. Adjustments can be made to the characteristics nanoparticles by differing degrees of substitution of sulfobutyl groups. In another case, a carboxylic end group of PLGA was conjugated to hydroxyl group of doxorubicin and formulated into nanoparticles. This modification produced a sustained release of the drug that was approximately six times longer than with unconjugated drug [33].

The molecular weight and concentration of the polymer used will also affect the nanoparticles. The molecular weight of the polymer has opposite effects on size and encapsulation efficiency. Smaller size nanoparticles, approximately 100 nm, can be prepared with lower molecular weight polymer, however, at the expense of reduced drug encapsulation efficiency. On the other an increase in polymer concentration increases encapsulation efficiency and the size of the nanoparticles [7, 9, 16]

When considering a particular polymeric nanoparticle for a given drug delivery application, particle size and encapsulation efficiency are two of the most important characteristics of nanoparticles. One should determine what the goal of the nanoparticle delivery system is before determining the size desired. For example if the goal is rapid dissolution in the body or arterial uptake then the size of the nanoparticles should be approximately 100 nm or less. If prolonged dissolution is required or targeting mononuclear phagocytic system (MPS), larger particles around 800 nm would be preferable. In one study, the encapsulation efficiency was maximized in the double emulsion solvent evaporation technique when the pH of the internal and the external aqueous phases were brought to the isoelectric point of the peptide being encapsulated, methylene chloride was used as a solvent, and the PLGA was rich in free carboxylic end groups [34].

Another characteristic of polymeric nanoparticles that is of extreme interest is zeta potential. The zeta potential is a measure of the charge of the particle, as such the larger the absolute value of the zeta potential the larger the amount of charge of the surface. In a sense, the zeta potential represents an index for particle stability. For the case of charged particles, as the zeta potential increases, the repulsive interactions will be larger leading to the formation of more stable particles with a more uniform size distribution. A physically stable nanosuspension solely stabilized by electrostatic repulsion will have a minimum zeta potential of 630 mV [35]. This stability is important in preventing aggregation. When a surface modification is added like PEG the negative zeta potential is lowered, increasing the nanoparticles stability [12].

3. Surface Modification

The surface modification, synthesis and choice of the nanoparticles are entirely dependent on nature of drugs, delivery periods, stability, permeability, release of drug, etc. [36]. In particular, the body recognizes hydrophobic particles as foreign and thus they are rapidly taken up by the MPS. However, if sustained systemic circulation is required then the surface of hydrophobic nanoparticles must be modified in order to prevent phagocytosis. Following intravenous administration, hydrophobic nanoparticles are rapidly cleaned from the systemic circulation by the MPS, ending in the liver or spleen [37]. It appears that the hydrophobic nature of most biodegradable particle would limit the applications. However, one may overcome concerns of clearance by the MPS through surface modification techniques. To further increase circulation time, the particles can be coated with molecules that provide them with a hydrophilic protective layer, such as poly-ethylene glycol, PEG, or poly-vinyl pyrrolidone (PVP). This static layer prevents macromolecules to interact with the particle, even at low surface coverage for particles to release their load at a specific site. The accumulation of drug-loaded nanoparticles at the target site is important instead of their circulation and retention in the circulatory system of the body. This can be ensured by passive or active targeting.

In of passive targeting, nanoparticles accumulate at tumor sites because of the leaky vasculature that often characterizes tumor tissue. In active targeting, the nanoparticles carry targeting molecules on the surface that are able to interact with the surrounding tissue. To increase the stability and long-term systemic circulation of nanoparticles, surface of conventional nanoparticles are modified [37]. Hydrophilic polymers such as PEG, poloxamers, polysorbate 80, TPGS, polysorbate 20, polysaccharides like dextran and different type of copolymers can be used to efficiently coat conventional nanoparticles surface leading to variation in the surface properties [38]. These coatings provide a dynamic cloud of hydrophilic and neutral chains at the particle surface, which repel plasma proteins. Surface modification by TPGS increases the adhesion of nanoparticles to tumor cells surface. It also provides milder environments to the encapsulated proteins. IgG coating on the surface of nanoparticles increases the immunoresponse of nanoparticles. Hydrophilic polymers can be introduced at the surface in two ways, either by adsorption of surfactants or by use of block or branched copolymers [37, 39].

4. Drug Loading & Release Mechanism

A successful nanoparticle system may be the one which has high loading capacity to reduce the quantity of the carrier required for administration. Drug loading into nanoparticles is achieved by two methods: one by incorporating the drug at the time of nanoparticle production and second by adsorbing the drug after the formation of nanoparticles by incubating them in the drug solution [40]. Drugs can be loaded onto nanoparticles by adding them to a solution that contains previously prepared nanoparticles or by adding them to the reaction mixture during the polymerization process [40]. These two methods provides solid solution for the drug encapsulation in the polymer, dispersion of the drug in the polymer, adsorption of the drug onto the surface of the nanoparticles and chemical binding of the drug to the polymer. The amount of bound drug and the type of interaction of drug and nanoparticles depend on the chemical structure of the drug as well as the polymer and the conditions of drug loading [41]. The determination of the adsorption isotherm is one possible way to detect the type of binding and the binding rate (mg drug/mg nanoparticle). Adsorption isotherms for the nanoparticle/drug delivery system is used to give vital information on the best possible formulation, the drug binding capacity onto the surface of nanoparticles and the drug adsorbed. Linear sorption isotherms characterize solid solutions and Langmuiror S-type isotherms characterize surface adsorption. Because nanoparticles are colloidal systems, precise determination of the drug content is a major problem. Therefore, the most reliable way to separate the nanoparticles from the solution containing unbound drug is ultracentrifugation or gel filtration. From the amount of drug bound, the encapsulation efficiency (EE) of the drug can be calculated by using the formula:

EE = Amount of drug bound/ Total amount of drug used for nanoparticle production

The drug release mechanisms are equally important as the drug polymer formulation because of the proposed application in sustained drug delivery. For manipulation of the rate and the timing of the drug release from nanoparticles, a good understanding of the mechanisms of drug release is needed. There are five possible methods for drug release: (a) desorption of drug bound to the surface, (b) diffusion through the nanoparticle matrix, (c) diffusion through the polymer wall of nanocapsules, (d) nanoparticle matrix erosion, or (e) a combined erosion–diffusion process [42]. The kinetic analysis of drug release from nanoparticles can be described by a biexponential function

$$C = Ae - t + Be - t$$

where C is the concentration of drug remaining in the nanoparticles at time t, A and B are system characteristic constants (A is used for diffusion control system and B for erosion control system), and are rate constants that can be obtained from semilogarithmic plots [42]. In general drug release rate depends upon solubility, diffusion and biodegradation of the matrix materials. The drug release mechanisms can be modified by the choice of polymer matrices. Drug release also depends upon the loading efficiency of drug and size of nanoparticles. Larger particles have a smaller initial burst release than smaller particles. The drug loading capacity is directly proportional to burst and release rate of nanoencapsulated drug molecule. In the case of nanospheres, where the drug is uniformly distributed, the release occurs by diffusion or erosion, of the matrix under sink conditions. If the diffusion of a drug is faster than matrix erosion the mechanism of release is largely controlled by a diffusion process. The rapid initial release or burst is mainly attributed to weakly bound or adsorbed drug to the large surface of nanoparticles [43]. The addition of other polymers to PLA based polymers can also be used to control drug release. For example, PEG has been polymerized into a PLA homopolymer creating a PLA–PEG–PLA copolymer [44]. The drug release continued to increase as the total molecular weight of the copolymers decreased. The initial burst can be decreased in the absence of lower molecular weight polymers

5. Application of Nanoparticles:

Protein and peptide delivery from PLA/PGA particulate systems:

Efforts are also continuing on delivery of proteins and peptides from biodegradable microparticles[45]. Controlled release of interleukin- 2 and variations from 50:50 PLA/PGA microspheres, on the order of 50-200 /zm in diameter, showed a burst of release, followed by a period of extremely low release for days 6-15, ending with nearly constant release through 30 days [46]. Thyrotropin-releasing hormone (TRH) release was studied from microparticles prepared from 75:25 PLA/PGA and 100% PLA [47]. The microparticles were prepared using a modified solvent evaporation system based upon a water/oil/water emulsion system and were approx. 50 ~m in diameter. The injection vehicle used was an aqueous solution containing 1% sodium carboxymethylcellulose and 0.5% Tween 80. Lower molecular weight polymers gave larger bursts of release of TRH and faster overall release (Mol. Wt 5000, 6000, 8000 and 11000). Drug release was faster than the polymer weight loss, indicating that the drug diffused through the channels formed in the polymer at advanced stages of degradation. Release of nafarelin (LHRH analogue) was found to follow a triphasic pattern with an initial burst, and then a low rate of release, followed by a higher rate of release in some early work carried out on this system [45] Microparticles of 50:50 PLA/PGA with 10-50 /xm diameters showed in vitro release for up to 40 days and in vivo activity for even up to 70 days. A similar system is now marketed worldwide and is known as the Lupron depot.

Delivery of anti-cancer agents from PLA/PGA particulate systems

Some studies have addressed the encapsulation of anti-cancer agents into PLA and PLA/PGA microparticles [48]. Aclacinomycin (or aclarubicin hydrochloride) is an anti-cancer agent which has many undesirable side effects such as nausea, vomiting, anorexia, leukocytopenia and thrombocytopenic toxicities. It would be desirable to target delivery of this drug to only cancerous tissues. Microspheres were prepared by traditional solvent evaporation methods using PLA in a variety of olecular weights (3600, 4000, 4800, 7200 and 10 000) [48]. The drug release rate was found to be strongly dependent upon both molecular weight and drug loading rate. Microparticles of higher molecular weight polymers showed release in vitro for more than 35 days. Adriamycin and cisplatin, other anti-cancer drugs, have also been encapsulated into PLA and PLA/PGA by traditional solvent evaporation methods [48]. These formulations were prepared with quite high drug loadings of 50-70 wt%, with in vitro release only lasting for up to 17 days.

Delivery of vaccines from PLA/PGA particulate systems

Another advantage of biodegradable drug delivery systems is that they can be designed to deliver vaccines in a number of pulses from a single injection of microencapsulated drug. A significant effort, in concert with the World Health Organization, is in place in a number of institutions to develop vaccine delivery systems for developing countries. For example, biodegradable microspheres of PLA/PGA 50:50 with only 1% of the toxoid vaccine of staphylococcal enterotoxin B (SEB) dramatically increased the circulating IgG anti-toxin toxoid when compared to free toxoid [49]. This study used a mixture of microspheres of 1-10 /zm and 20-50/zm. This mixture gave an initial release from the smaller microspheres and a later release from the population of microspheres with the larger size. They were administered by intraperitoneal injection in mice. Higher antibody levels were seen for at least 90 days upon a single injection of the mixed population of microspheres. The response of the microparticles of size less than 10/zm after injection appears to be both a depot effect as well as because of the rapid phagocytosis of the microspheres by antigen-presenting accessory cells such as T cells. Other efforts include development of oral delivery systems based upon biodegradable microparticles [50]. Orally administered microspheres, containing SEB toxoid, of 1-10 /zm are taken up by Peyer's patch lymphoid tissue of the gut, and those of size 5-10 /.~m can remain there for up to 35 days, providing controlled release. Some studies have also been conducted using the diphtheria toxoid delivered with PLA microparticles of Mol. Wt 49 000 [51]. These formulations have shown release up to 75 days in vivo, comparable to traditional treatment requiring three injections as opposed to a single effective injection with microparticle formulation. The microparticles prepared by a variation of the solvent evaporation method, were implanted subcutaneously and were of the size 30-100/~m.

Other forms of PLA/PGA used for drug delivery

Recent work has been reported with tablets or slabs of PLA/PGA [52, 53, 54, 55] including analysis of drug release kinetics from slabs with and without surrounding rate limiting membranes [56] and the effect of the polymer glass transition and molecular weight of the drug release behaviour of theophylline [52]. Release of albumin from rods prepared from PLA/acetone suspensions which were then coated with pure PLA was found to be most strongly dependent upon the geometry of the system (rod length compared to cross-sectional area) and drug loading [53]. Melt-pressed formulations of calcitonin with PLA showed an initial burst of drug release and complete release within 3 days for polymers of Mol. Wt 1400, and 24 days for Mol. Wt 4400 [56]. A long-term degradation study of PLA in vivo was conducted using rods and blocks of high molecular weight PLA (120 000, 200 000 and 429000) (rods 25 x 3 x 2 mm, blocks 3 x 3 x 2 mm) which were implanted into the dorsal muscle of rats (Pistner et al., 1993). The lower specimens were totally degraded with 1 year and the moderate molecular weight specimens nearly degraded in 2 years. All polylactides were incorporated well, forming a collagenous fibrous layer without tissue irritation. Vert et al. have evaluated the biocompatibility of biodegradable polymers and the mechanism of drug release from them [57, 58]. It has been found that the initial degradation of the polyesters is hydrolytic, and that during the latter stages, enzymatic degradation may also take place [57]. The release of drug from these degrading polymers is a combination of diffusion and degradation, which each mechanism predominating at a specific time in the degradation of the polymer [58]. Initial drug release may be in large part due to diffusion, depending upon the drug that is releasing. The increase in release rate often seen with drug release from biodegradable microparticles is due to the kinetics of the polymer weight loss after bulk hydrolysis has progressed to a point where there is measurable weight loss from the polymer instead of simply a decrease in the average molecular weight as occurs early in the biodegradation process.

PLA/PEG and PLA/PEO block copolymers for drug delivery

Some work has also been performed to combine poly(ethylene glycol) and poly(lactide-co-glycolide) s in the same drug delivery formulation. The research groups that have addressed this opportunity have usually taken the route of preparing block copolymers of PLA and PEG or PEO [59, 60]. Much of this work has been spurred by the fact that PEG is non-toxic and has been cleared by the US Food and Drug Administration for internal use in the human body [60]. Release in vitro of norethisterone (30 wt% drug) from copolymers of PLA and PEG showed no greater a burst of release than from PLA alone and a significantly higher rate of release, when compared to PLA alone, from that point on. Block copolymers of PLA and PEO have been investigated with the aim of developing a new family of biodegradable polymers [59]. These new polymers ranged from 20 to 84% PLA and the PEO chains were of Mol. Wt 600-6000 (which in reality qualify them as PLA/PEG copolymers). The incorporation of the PEO into the polymer yielded a highly hydrophilic material, with equilibrium water contents higher than 60%. For hydrolytically sensitive drugs such as proteins, this type of material is usually not desirable because the stability of the drug may often be compromised when in such a water-filled environment. PLA/PGA polymers are excellent for protein and peptide release because of their hydrophobic nature which serves to protect the drugs from the fluid in the in vivo environment and thus increase their stability as well as control their release. These new copolymers were successful, however, in combining the material strength and hydrophobicity of the PLA with the elasticity and hydrophilicity of the PEO but no drug delivery data was presented. Studies have shown that subcutaneously administered nanoparticles are taken up by the lymph nodes [61]. PEG attached to individual drug molecules has been shown to significantly increase the drug circulation time because of the masking effect of the PEG and its resulting lack of uptake into the reticulo-endothelial system [62]. PEG is the most extensively studied method for extending circulating half-life of proteins [63]. PEG is a linear, uncharged, hydrophilic, nonimmunogenic molecule that has been used to modify a large number of compounds, including trypsin, superoxide dismutase, catalase, adenosine deaminase, bovine serum albumin, asparaginase, uricase, lipase, hemoglobin, interleukin-2 and arginase. At least six PEG-enzyme conjugates have reached clinical trials: PEG-adenosine deaminase (for severe combined immunodeficiency disease, SCID); PEG-antigen E (for ragweed hay fever); PEG-asparaginase (for acute lymphoblastic, lymphocytic and undifferentiated leukemias and for lymphomas); PEG-honeybee venom (for reperfusion injury associated with organ transplantation); and PEG-uricase (for hyperuricema associated with chemotherapy or gout). For use in magnetic resonance imaging contrasting agents, liposomes were studied which were unmodified as well as surface modified with dextran or PEG. PEG-modified liposomes showed an imaging efficiency of more than twice that of the other liposomes. PEG-coated 'stealth' nanospheres have been prepared by using diblock copolymers of

PLA/PGA and PEG (Mol. Wt 350-20000) [64]. During preparation of the nanoparticles, using solvent evaporation techniques, the PEG segment migrates to the surface of the particles, leaving it 'covered' with a PEG layer. Particles thus prepared were on the order of 200 nm in diameter. After injection of plain or modified nanospheres (using Indium radioactivity tracking) 5 min after injection 40% of the unmodified nanoparticles were found in liver and 15% in blood. Modified nanoparticles, however, showed 15% in the liver and 60% in the blood with a significantly improved circulating time. Plain nanospheres completely disappeared from blood in 4 h, but at that same time approx. 30% of modified nanospheres were still circulating. Delivery of antisense oligonucleotides using an injectable polymer composed of PEG chains with a degradable oligo-lactide segment and reactive acrylate segment on each end has also been studied recently [65].

CONCLUSION

Nanoparticulate drug delivery systems seem to be a viable and promising strategy for the biopharmaceutical industry. They have advantages over conventional drug delivery systems. They can increase the bioavailability, solubility and permeability of many potent drugs which are otherwise difficult to deliver orally. Nanoparticulate drug delivery systems will also reduce the drug dosage frequency and will increase the patient compliance. In near future nanoparticulate drug delivery systems can be used for exploiting many biological drugs which have poor aqueous solubility, permeability and less bioavailability. Nanoparticles can minimize some of these drugs unique problems by safeguarding stability and preserving their structure. In addition, nanoparticles provide ingenious treatment by enabling targeted delivery and controlled release.

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