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Current advances in sustained-release systems for parenteral drug delivery

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Major progresses in the development of parenteral sustained-release systems have been made in recent years as evidenced by the regulatory approval and market launch of several new products. Both the availability of novel carrier materials and the advances in method of fabrication have contributed to these commercial successes. With the formulation challenges associated with biologics, new delivery systems have also been evolved specifically to address the unmet needs in the parenteral sustained release of proteins. In this review paper, different new carriers systems and preparation methods are discussed with special focus on their applications to biologicals.

Keywords: biodegradable polymer, chemical conjugation, implant, *in situ* gelling system, lipid microparticle, liposome, micro- and nanoparticulate systems

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1. Introduction

Parenteral drug delivery is the administration of a drug via a parenteral route usually by the means of intravenous, subcutaneous or intramuscular injection. The delivery of a drug locally to a specific site of the body such as by epidural and intra-articulate injection, as well as implantation of a product subcutaneously or into a body cavity by surgical procedures, represent other modes of parenteral drug delivery. The invasive nature of parenteral drug delivery is well recognised as its major drawback. However, even with the recent advances in other noninvasive pain-free alternative delivery approaches, such as transdermal, pulmonary and nasal drug delivery, the therapeutic use of certain drugs, particularly proteins and peptides, can only be realised when delivered parenterally. This is simply because of their poor mucosal membrane permeability and/or instability in the delivering environment (i.e., gastrointestinal tract).

Sustained-release systems are designed to extend or prolong the effect of a drug at the site of action. Some distinct therapeutic advantages offered by such a system include reducing dosing frequency, maximising the efficacy–dose relationship, decreasing adverse side effects and enhancing patient compliance. Among these advantages, the alleviation of pain associated with frequent injection can be the most desirable feature of a parenteral sustained-release system from the patient's point of view. The cost of parenteral drug treatment can be significantly reduced because of less frequent medical attention needed for parenteral administration. The requirement of a lower amount of drug in a sustained-release system as compared with multiple single dosing can be another major cost-saving measure particularly for a costly drug such as a therapeutic protein.

The efficacy of some drugs can be considerably improved when delivered in a sustained-release form for either a systemic or local therapeutic effect. The improved tumouricidal activity of doxorubicin encapsulated in pegylated liposomes (Stealth®, Alza Corp.) has been attributed to the extended blood circulation times of the drug in the carrier, and the resultant enhanced extravasation and accumulation within

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solid tumours [1]. The direct implantation of a sustained-release system (a depot) at the site of action for a local therapeutic effect can lead to a significantly higher local drug concentration while minimising systemic exposure to the drug and its associated toxic effect. Such a concept is better demonstrated by the use of a biodegradable polymeric implant containing carmustine for the treatment of brain cancer and a biodegradable implant containing gentamicin for the treatment of osteomyelitis [2,3].

Safety issues relating to a parenteral sustained-release system cannot be overlooked. Premature termination of treatment in case of drug toxicity can be extremely difficult for most of the parenteral sustained-release systems once administered. The adverse response of local tissues to the drug and/or the system on prolonged exposure can be clinically alarming. The sterility and pyrogen-free requirements for a parenteral product add additional challenges and cost in the development and manufacturing of a sustained-release product for parenteral delivery.

Parenteral sustained-release technologies with differing complexities have been developed in the past and continue to evolve. A relatively water-insoluble drug can be simply formulated into an aqueous or oil suspension as a sustained-release product for subcutaneous or intramuscular injection. However, the majority of drugs that are candidates for parenteral sustained-release formulations are water soluble, thus the release of the drug ought to be controlled with the use of less soluble materials for drug entrapment or encapsulation. These materials are called carriers for the drug when a delivery system is formed. Carriers used for parenteral sustained-release delivery are very diversified in terms of chemical compositions and physicochemical properties, which are the determining factors on the physical form, level of drug loading, chemical and physical stability, and mode of administration of the final delivery system. In recent years, the research in parenteral sustained-release technologies has been fuelled mainly by the advent of novel carriers. The growing significance of parenteral sustained-release products in the pharmaceutical marketplace is also evidenced by the increasing number of products that have been granted regulatory approval during the last 5 years (Table 1). This review focuses on the recent progress in the development of parenteral sustained-release systems using novel carriers.

2. Polymeric micro- and nanoparticulate systems

Many of the currently approved parenteral sustained-release products are polymeric microsphere formulations that can be injected subcutaneously or intramuscularly for systemic effect or injected into a specific body site for localised treatment. Although the injection of microspheres is not pain free and reconstitution is often required, the procedures are much less complicated as compared with implantation. Due to the non-retrievable nature of microspheres after administration, carriers used in a microsphere formulation are biodegradable and biocompatible. A variety of biodegradable polymers available for microsphere formulations are mostly prepared synthetically. The greatly diversified chemical structures/compositions of these polymers have allowed the fabrication of microspheres with a wide range of product characteristics tailored to a specific therapeutic need, such as drug loading, release rate and duration of action. The manufacturing processes of microspheres are not straightforward and usually involve the use of customised equipment. The use of organic solvents can make the process even more complex and costly because of the need for solvent removal from the product to meet the allowable residual limits and also for solvent recycling in order to comply with regulations on emission to the environment. Because terminal sterilisation is not typically feasible, aseptic processing is the only option. This can be very expensive and adds cost to the final product. High product loss associated with some manufacturing methods such as spray drying or spray congealing can be an issue for an expensive drug. The recent advances in the use of different types of biodegradable polymers for the development of microsphere and nanoparticle products are discussed below.

2.1 Lactide/glycolide polymers

Poly(lactic acid) (PLA), polyglycolic acid and poly(lactic-co-glycolic acid) (PLGA) are the most commonly used biodegradable polymers in formulation of microspheres primarily because of the long safety history for their use in medical products (e.g., bioabsorbable sutures). The early successes of PLGA microsphere products can be exemplified by the approval and commercialisation of several sustained-release (1 – 4 months) peptide formulations such as leuprolide (Lupron Depot®, TAP), octreotide (Sandostatin LAR®, Novartis) and triptorelin (Trelstar®, Debiopharm). Nutropin Depot® (Genentech) is the first approved PLGA microsphere product of a protein (recombinant human growth hormone [rhGH]), which was launched in 2000, but its sale was discontinued in 2004. The development of PLGA microsphere formulations of small molecules can be represented by Risperdal Consta® (Johnson & Johnson), which provides a 2-week sustained release of risperidone for the treatment of schizophrenia. Many more PLGA microsphere products have been under evaluation for the sustained release of small molecules [4-6], peptides [7-9], vaccines [10] and proteins [11].

The PLGA copolymers are highly hydrophobic and possess a relatively high glass transition temperature (45 – 55°C). Hence, the copolymers are dissolved in an organic solvent prior to being further processed with the drug using different encapsulation methods. A single emulsion method can be applied when the drug is dissolved or dispersed in an organic solvent solution of the copolymer. Microspheres prepared by this method are matrix systems with the drug uniformly distributed in the polymeric matrix. If the drug is dissolved in an aqueous solution, it can be encapsulated via a double emulsion method (water/oil/water). The removal of the organic

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Table 1. Recently approved parenteral sustained-release products (January 2000 – August 2005).

Delivery system	Product (drug)	Carrier	Indication	Company	Year
Polymeric microparticular system	Risperdal Consta® (risperidone)	PLG microspheres	Schizophrenia	Alkermes/Janssen (Johnson & Johnson)	2003
	Trelstar® LA (triptorelin pamoate)	PLG microspheres	Advanced prostate cancer	Debio RP	2001
	Plenaxis® (abarelix)	CMC complex	Prostate cancer	Praecis	2003
Lipid system	DepoDur® (morphine sulfate)	Depofoam™	Postoperation pain management	SkyePharma	2004
In situ depot-forming system	Eligard® (leuprolide acetate)	PLG gel	Advanced prostate cancer	QLT (formally Atrix)	2002
Implantable system	Vantas® (histrelin)	Hydrogel implant	Advanced prostate cancer	Valera	2004
	Viadur® (leuprolide acetate)	Titanium implant	Advanced prostate cancer	Alza Corp.	2000
	Impanon® (levonorgesterol)	Silicone rubber implant	Contraception	Organon	2004
Chemical conjugation	Somavert® (pegvisomant)	Pegylation	Acromegaly	Pfizer	2003
	Aranesp™ (darbepoetin-α)	Pegylation	Anaemia	Amgen	2003
	Pegasys® (PEG-IFN-α_{2a})	Pegylation	Chronic hepatitis C	Roche	2002
	PEG-Intro® (PEG-IFN-α_{2b})	Pegylation	Chronic hepatitis C	Schering-Plough	2001

CMC: Carboxymethylcellulose; IFN: Interferon; PEG: Polyethyleneglycol; PLG: Poly(lactic-co-glycolic acid).

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solvent can be achieved either by solvent evaporation or solvent extraction. Spray drying has also found its application in microsphere fabrication. The particle-size distribution of microspheres formed by these conventional methods is usually very broad, which can result in products with inconsistent release profiles. An ink jet technology has been developed allowing the preparation of PLGA microspheres with uniform particle-size distribution (Figure 1) [12]. The technology involves the dispensing of a small amount of drug–PLGA–methylene chloride solution into a 0.1% polyvinyl alcohol solution in a controlled fashion through the use of a piezoelectric device. After the organic solvent is removed by evaporation, hardened drug-loaded microspheres with uniform size distribution were collected.

Proteins are prone to degradation during encapsulation when prolonged contact with an organic solvent is required. An anhydrous spray freeze-drying process was developed (ProLease®, Alkermes) [13]; solid protein particles are mixed with a methylene chloride solution of PLGA and the suspension is sprayed into frozen ethanol overlaid with liquid nitrogen. On warming to -70°C, ethanol is liquefied and methylene chloride is extracted by ethanol from the polymer phase. Nutropin Depot is a PLGA microsphere product manufactured by the ProLease process. The high cost of the process may have caused the discontinued commercialisation of this product in 2004. PolyShell® (Akina) is a new process developed for the encapsulation of proteins. This process involves the use of a coaxial ultrasonic atomiser to generate microcapsules where the aqueous core of a dissolved drug is coated with a thin layer of PLGA liquid membrane due to the difference in surface tension of these two solutions (Figure 2). The microcapsules formed are collected in a 0.15% PVA solution for hardening. Reservoir-type PLGA microcapsules of lysozyme were prepared and showed of a zero-order release kinetics with no loss in functional integrity [14].

Supercritical carbon dioxide ($scCO_2$) is nonflammable, nontoxic, noncorrosive and has a low critical point (critical temperature 31.1°C, critical pressure 73.8 bar). These unique properties have made it a very attractive processing medium for heat-liable proteins. A gas antisolvent method involving the use of $scCO_2$ has been reported for the encapsulation of insulin in PLA microspheres. In this process, a solution of PLA and insulin/polyethyleneglycol (PEG) in an organic solvent was atomised through a nozzle into a vessel containing compressed CO_2, which caused the precipitation and formation of the insulin–polymer microspheres. Insulin

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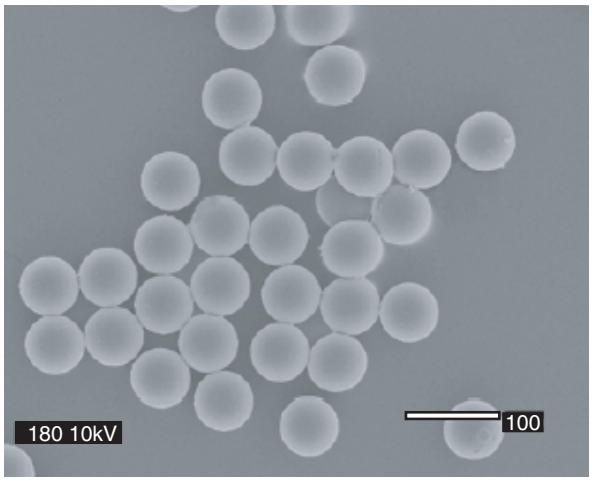

Figure 1. Scanning electron microscopy of microspheres prepared by ink jet technology. Image provided by the courtesy of D Radulescu at MicroFab Technologies.

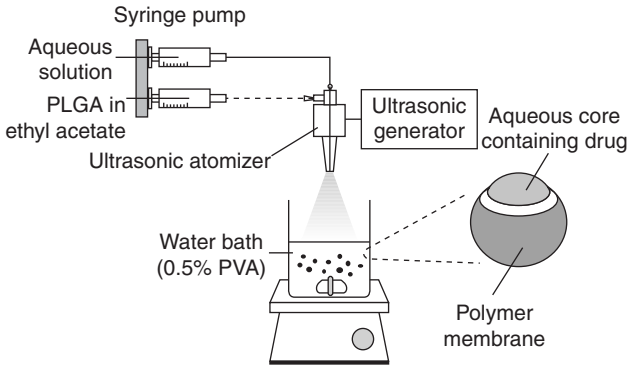

Figure 2. Schematic description of the microencapsulation system using a coaxial ultrasonic atomiser. In the present example, liquid 1 is an aqueous solution and liquid 2 is a PLGA–ethyl acetate solution. Reprinted from YEO Y, PARK K: A new microencapsulation method using an ultrasonic atomiser based on interfacial solvent exchange. *J. Control. Release* (2004) **100**(3):379-388 [14], copyright (2004) with permission from Elsevier.
PLGA: Poly(lactic-co-glycolic acid); PVA: Poly(vinyl alcohol).

entrapped in the microspheres was found to retain > 80% of its hypoglycaemic activity [15,16]. A supercritical fluid mixing encapsulation method based on the ability of $scCO_2$ to plasticise the polymer has also been reported [17,18]. Unlike the antisolvent method, organic solvent is not required in this method. Solid drug particles and polymer particles are mixed in $scCO_2$ in a vessel. The polymer is plasticised and swollen with a significant lowering in viscosity, allowing efficient incorporation of the drug particles into the polymer matrix. The subsequent spraying of the drug/polymer mixture through a nozzle into a collection chamber filled with nitrogen results in the formation of drug-loaded microparticles. Maintenance of the functional activity of several proteins encapsulated in the polymer by the supercritical mixing process has been demonstrated.

Block copolymers consisting of PLGA as the hydrophobic block (A) and polyethyleneoxide (PEO) or PEG as the hydrophilic block (B) have been prepared for evaluation as microparticulate carriers for the delivery of hydrophilic molecules such as proteins [19,20]. Microspheres of erythropoietin were prepared with PLGA–PEO–PLGA (A–B–A) triblock copolymers and evaluated for protein stability and *in vitro* sustained release [21]. Star- and brush-like grafted PLGA using either hydrophilic multiarm PEOs or charged, hydrophilic polyelectrolyte backbones were also developed and investigated as carriers for protein delivery [22,23]. Nanoparticles of PEG–PLGA diblock copolymers were reported to exhibit prolonged circulation time in the blood and to show promise as an intravenous sustained-release system for proteins [24]. Because of the novel properties of these block copolymers, the advantages of pegylated microspheres and nanospheres as the carriers for parenteral sustained-release delivery of proteins are well recognised, and their applications have been further explored [25].

2.2 Polycaprolactones

Poly-ε-caprolactone (PCL) is a biodegradable semicrystalline polyester that exhibits slow degradation and is suitable for sustained release extending to a period of > 1 year. The encapsulation of a variety of drugs including antigens, antihypertensive drugs, chemotherapeutic agents and antibiotics in PCL microspheres for effective delivery has been extensively reviewed [26]. Unlike polymers and copolymers based on lactides and glycolides, the degradation of PCL will not result in an acidic microenvironment that is detrimental to the stability of proteins. Microencapsulation techniques have been developed to allow the incorporation of proteins into PCL polymers under mild conditions [26]. PCL microspheres of insulin were prepared and shown to maintain constant plasma drug concentrations over a prolonged period of time for effective control of blood sugar levels in rats [27]. Block copolymers of caprolactone with PLA, PLGA, PEG or PEO, which are more compatible with proteins and peptides, have also been evaluated for drug delivery [28-30].

2.3 Polyphosphoesters

Polyphosphoesters (PPE), a family of biodegradable polymers, have been investigated as carriers for sustained delivery of low molecular weight drugs [31], proteins [32] and DNA [33]. Recent research efforts have been reported on the development of polylactide-co-ethylphosphate, which is a copolymer of PPE and PLA, as drug carriers in several preclinical and clinical studies [34]. The degradation of this copolymer is characterised by a rapid degradation of the more labile and hydrophilic

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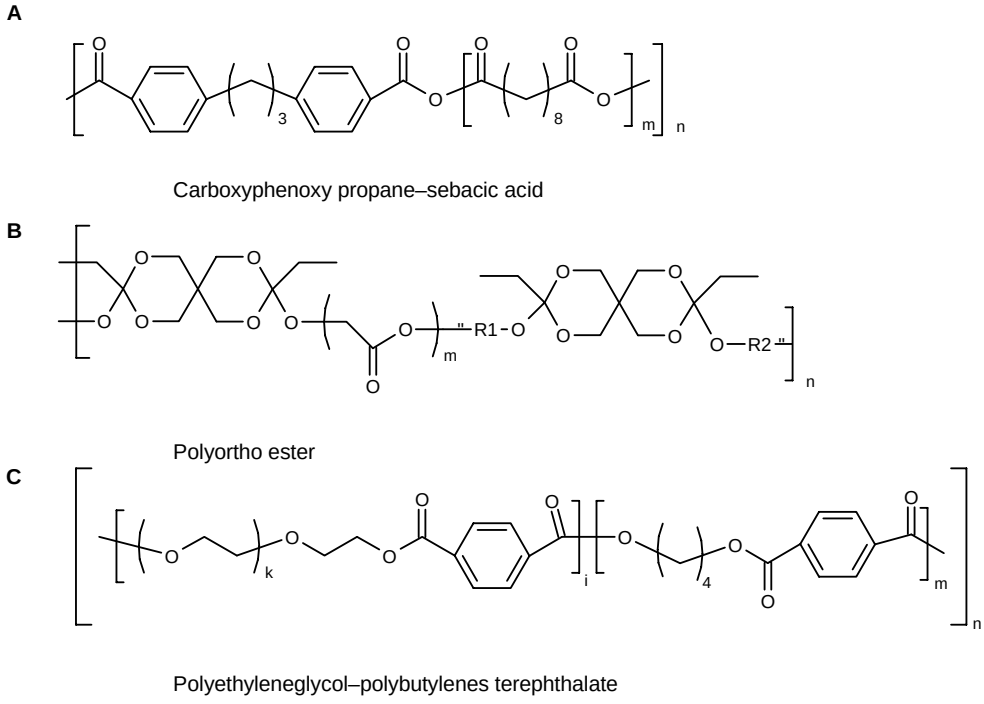

Figure 3. Chemical structures of carboxyphenoxy propane–sebacic acid [141]**, polyortho ester** [142] **and polyethyleneglycol–polybutylenes terephthalate** [143]**.**

phosphate groups followed by the slow degradation of the lactide bonds. Paclimer® (Guilford Pharmaceuticals) is a poly(lactide-co-ethylphosphate) microsphere formulation of paclitaxel for sustained release of the drug for treatment of ovarian cancer. Data from a Phase I trial in ovarian cancer patients show that the Paclimer microspheres administered by intraperitoneal injection produced an 8-week delivery of paclitaxel at a therapeutic level of 0.1 – 2.0 ng/ml [301].

2.4 Polyanhydrides

Polyanhydrides are biodegradable copolymers that are prepared by the condensation reaction of two fatty acids to form a hydrophobic backbone with hydrolytically labile anhydride linkages (Figure 3A). The applications of these type of copolymers, particularly as localised drug carriers for parenteral delivery have been recently reviewed [35,36]. By varying the type of fatty acids (hydrophobic or hydrophilic) and their ratios, the degradation rate of the polymer can be controlled to provide drug release duration from weeks to months. Polyanhydrides mainly undergo surface erosion and thus better protect the unreleased drug from the potential destabilising effect of the releasing medium. Owing to the low melting point and good organic solvent solubility, polyanhydride microspheres can be fabricated by using different techniques, such as spray drying, hot-melt encapsulation and emulsion methods [35]. Polyanhydrides, especially those derived from sebacic acid (SA), 1,3-*bis*(*p*-carboxyphenoxy) propane (CPP) and fatty acid dimer, have been investigated as carriers for parenteral sustained release of a variety of therapeutic agents, including local anaesthetic agents, anticancer agents, antibiotics, anticoagulants, anti-inflammation agents, neuroactive drugs and growth hormone [35].

2.5 Polyortho esters

The polyortho esters (POEs) are synthesised by the condensation of diols and a diketene acetal. The hydrolytic degradation of the ortho ester linkages can be controlled by the copolymerisation with a latent acid, such as glycolic acid and lactic acid [37]. The latent acid segments are readily hydrolysed to generate acid, which can further catalyse the hydrolysis of ortho ester linkages in the polymer backbone. This new class of POE is called Biochronomer® (Figure 3B), which is proprietary and developed by AP Pharma. The excellent stability of POEs has been demonstrated by studies showing that the polymer was stable while being irradiated at 24 kGy and stored at room temperature under anhydrous conditions [38]. The POEs are thermoplastic polymers that can be easily fabricated into microparticles using an extrusion method followed by cryogenic milling. The activity of bovine serum albumin was retained in thin strands of a POE polymer that were extruded with the protein at 75°C [39]. A spray congealing process with the use of a spinning disk technology was developed for the preparation of POE microspheres of bupivacaine for prolonged local anaesthetic effect [40]. Because POEs are soluble in most commonly used organic solvents, microspheres can be prepared via an emulsion–solvent evaporation method, although low encapsulation efficiency was reported with some water-soluble drugs [41,42]. The release of

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drug from a POE polymer matrix is controlled by the surface erosion of the polymer and characterised with a significant lag time that can be reduced or eliminated with the addition of a small amount of PEG to the polymer prior to extrusion [39]. Block copolymers of POE and PEG were also prepared and shown to produce microspheres with high encapsulation efficiency with water-soluble compounds [43].

2.6 Block copolymers of polybutylene terephthalate

A series of polyether ester multiblock copolymers, based on hydrophilic PEG and hydrophobic polybutylenes terephthalate (PBT), has been developed and commercialised by OctoPlus as PolyActive® (Figure 3C). The degradation of the polymers occurs by hydrolysis of the ester bonds and oxidation of the ether linkages [44]. By varying the amount and length of each of the two building blocks, the rate of polymer degradation and swelling can be precisely controlled; a high PEG content results in faster copolymer degradation [45]. The PEG/PBT copolymers are shown to be biocompatible and biodegradable [46]. In 2000 the copolymer was approved by the FDA for use in bone replacement application. The PEG/PBT microspheres containing lysozyme were prepared with high entrapment efficiency by a double emulsion–solvent evaporation method. *In vitro* release of the protein from the microspheres was shown to sustain for almost 1 month [47]. A microsphere formulation of recombinant human IFN-α (Locteron™, OctoPlus) is under development for the treatment of hepatitis C. Results from preclinical studies have shown that the IFN-α levels in plasma can be sustained for a period of to 2 weeks with a single injection of the microspheres [302].

2.7 Crosslinked dextran

A biodegradable hydrogel system based on crosslinked dextran has been developed as a proprietary drug delivery system by OctoPlus. The hydrogel in the form of microspheres has been found to be particularly suitable for protein delivery as the microspheres are formed in a completely aqueous medium [48]. OctoDEX® is a modified dextran that is derivatived with hydroxyethyl methacrylate (dex-HEMA) [49]. An aqueous solution of dex-HEMA and protein is added in a PEG solution and a catalyst-initiated polymerisation of the conjugated groups attached to the dextran molecule results in the crosslinking of the dextran chains and formation of microspheres. The particle size, crosslink density, initial water content and pore size of the microspheres are influenced by the composition of the starting materials, such as PEG molecular weight and concentration, dextran molecular weight, the degree of substitution of the crosslinking groups and their concentration [50,51]. The release of proteins from crosslinked dextran microspheres can be tailored from days to months [48,52]. Sustained therapeutic activity of recombinant IL-2-loaded microspheres was demonstrated in a mouse tumour model [53]. In a clinical study, after a single subcutaneous injection of hGH-loaded microspheres, prolonged release of the drug was achieved for 2 weeks without initial burst release. Increased levels of insulin-like growth factor-1 (IGF-1) and IGF-binding protein-3 were also observed during the period of release, indicating that the activity of hGH was maintained *in vivo* [302]. Excellent biocompatibility of the crosslinked dextran microspheres has been demonstrated in rats [54].

2.8 Polyamino acid polymers

Polyamino acid polymers based on L-leucine (Leu) and L-glutamate (Glu) have been developed by Flamel as drug delivery systems for proteins. An amphiphilic block copolymer composed of these two amino acids is called Medusa I® [55]. This copolymer forms self-assembled nanoparticles in water with poly-Leu chains packed inside the structure and poly-Glu chains exposed to water. The nanoparticles are 200 nm in diameter and composed of 95% water and 5% of the copolymer. Proteins are associated with the nanoparticles via noncovalent interaction. Following subcutaneous injection, the bound protein molecules are released slowly for up to 2 days by competitive replacement with serum proteins. Basulin®, a long-acting native insulin formulated with Medusa I is in Phase IIb clinical trial for the treatment of Type 1 diabetes. An amphiphilic block copolymer of hydrophobically modified poly-L-glutamate (Medusa II®) was developed for long duration of protein release for up to 2 weeks. This block copolymer self-assembles into submicron structures with the hydrophobic grafting forming hydrophobic nanodomains and the hydrophilic glutamate chains extending out. Long-acting formulations of IFN-α_{2b} and IL-2 are prepared with this copolymer and both are in Phase I/II clinical trials [303].

2.9 Cellulosic polymers

Carboxymethylcellulose (CMC) is a water-soluble anionic polymer that forms water-insoluble complexes with water-soluble cationic peptides through ionic interaction. By using the complexing capability of CMC, Praecis has developed a drug delivery technology, know as Rel-Ease®. The formation of insoluble CMC complexes can be optimised by pH, ionic strength, temperature and solution polarity [201]. The complex is prepared by simple mixing of an aqueous solution containing CMC and the drug until the complex precipitates. Plenaxis®, an injectable suspension of abarelix–CMC complex was developed based on the Rel-Ease technology. The efficacy of the 1-month depot formulation in patients with advanced prostate cancer has been demonstrated in clinical studies [56]. Plenaxis was approved by the FDA in November 2003 for the treatment of advanced prostate cancer; however, the commercialisation of the product was halted in May 2005 due to financial consideration [304].

2.10 Crosslinked albumin

A protein-matrix based drug delivery system called ProMaxx® (Epics/Baxter) has been developed for protein delivery. The microspheres are produced entirely in an aqueous medium by mixing a carrier protein (e.g., human serum albumin), a water-soluble polymer (e.g., hetastarch), a polyanionic polysaccharide

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(e.g., dextran sulfate, heparan sulfate and polyglutamic or polyaspartic acids), and a divalent metal cation (e.g., Ca^{2+} and Mg^{2+}). The resulting microspheres are further stabilised by reacting with a chemical crossslinking agent (e.g., 1-ethyl-3-[3-dimethylamino-propylcarbodiimide]) or exposing to heat. A therapeutic agent is added to an aqueous suspension of microspheres and the resulting drug-loaded microspheres are further stabilised by repeated exposure to a crosslinking agent or heat [202]. The microspheres exhibit a smooth surface and uniform spherical shape with particle size in the range of 0.5 – 40 µm. The release characteristics of the microspheres can be modified by changing the water-soluble polymer concentration, reaction temperature, pH, protein concentration and length of heat exposure of the microspheres. LeuProMaxx® (Baxter), the 1- and 3-month sustained-release microsphere formulations of leuprolide, are in Phase II clinical trial for the treatment of advanced prostate cancer.

3. Lipid micro- and nanoparticulate systems

Conventional lipid systems for parenteral sustained-release drug delivery include oil solutions and suspensions as well as emulsions for subcutaneous or intramuscular injection. The incorporation of a lipid-soluble drug in these systems is quite straightforward and the release of the drug is mainly controlled by the partition of the dissolved drug from the oil vehicle to the aqueous environment at the injection site. However, when a water-soluble drug is considered, these systems may find limited applications. Advanced lipid particulate systems with various degrees of structural complexity have been developed for parenteral sustained release of water-soluble and -insoluble drugs. In addition to subcutaneous and intramuscular injection, lipid particulate systems in submicron size (nanosystems) can be given intravenously, whereas some of the lipid systems are designed for epidural or intrathecal administration. Natural and synthetic phospholipids with or without further chemical modifications are the major structural components of lipid vesicles. Phospholipids have also been used as a physical stabiliser for lipid formulations composed of triglycerides. In general, the duration of sustained release provided by a lipid system, particularly lipid vesicles, is seldom longer than 1 week, which is significantly shorter than that achieved with a polymeric particulate system.

3.1 Liposomes

Liposomes are lipid vesicles composed of phospholipid bilayers and an inner aqueous core. A hydrophilic drug is entrapped in the aqueous space, whereas a hydrophobic drug can be intercalated into the bilayer. The composition of the lipid bilayer, the size and charge of liposomes, and the composition of the internal aqueous space can be optimised to enable efficient incorporation of a wide variety of drugs [57]. Liposomes are suitable for intravenous delivery, but they are preferentially taken up by phagocytic cells of the mononuclear phagocyte system (MPS) mainly in the liver and spleen following intravenous administration [58]. When the drug is not targeted at the MPS cells, the extensive uptake of liposomes by MPS cells results in the degradation of encapsulated drug, which not only reduces the therapeutic efficacy, but also poses potential toxicity to these cells [59].

The prolongation of the residence time of liposomes in the bloodstream becomes the prerequisite for using liposomes as an intravenous sustained-release carrier. Phospholipids with the attachment of PEG have been used to formulate liposomes with a more hydrophilic surface [60]. Pegylated liposomes were shown to prolong circulation in blood, reduce hepatosplenic uptake and expand tissue distribution [61]. The prolonged circulation time and improved pharmacokinetics of pegylated liposomal systems have been demonstrated for a variety of therapeutic agents such as docetaxel [62], vasoactive intestinal peptide [63] and cytokines [64,65]. Taking advantage of the enhanced permeability and retention effect associated with solid tumour and infected tissue, pegylated liposomes have been extensively investigated for delivering anticancer drugs and anti-infective agents via this passive targeting mechanism [66]. Doxorubicin HCl liposome injection (Doxil®, Alza Corp.) is the first pegylated liposomal product of doxorubicin approved for the treatment of refractory ovarian cancer and AIDS-related Kaposi's sarcoma. Other approaches in extending the circulation time of liposomes by attaching glycolipids, gangliosides or sialyl derivatives to the surface of liposomes have also been reported. Studies have shown that anticancer agents including adriamycin, vincristine and 5′-*O*-diacylphosphatidyl derivative of 2′-C-cyano-2′-deoxy-1-β-D-arabino-pentofuranosylcytosine encapsulated in palmityl-D-glucuronide liposomes were effective for cancer treatment [67].

The prolonged circulation time of pegylated liposomes has made it possible to develop immunoliposomes for active targeting of cancer cells. Immunoliposomes are prepared with ligands or monoclonal antibodies or antibody fragments attached to the surface of liposomes. These surface groups can bind selectively to antigens or receptors that are uniquely expressed or overexpressed on the cancer cells leading to the delivery of a drug to these targeted cells [68]. Positive results on the efficacy of immunoliposomes in various animal cancer models have been published [69]. New liposomal delivery systems formulated with new types of phospholipids such as cardiolipin (NeoPharm) and sphingomyelin (Inex) have been evaluated for the delivery of chemotherapeutic agents [70-72]. In clinical trials, these products have exhibited prolonged residence time in the bloodstream, enhanced physical stability, improved entrapment efficiency, and increased cancer-targeting specificity [305,306].

The development of liposomes as sustained-release systems for subcutaneous and intramuscular injection has been extensively documented in the literature [73]. The efficacies of the encapsulated drugs have also been demonstrated in various animal disease models. In spite of the proven efficacy and excellent tissue biocompatibility of the lipid components in a liposomal formulation, liposomes

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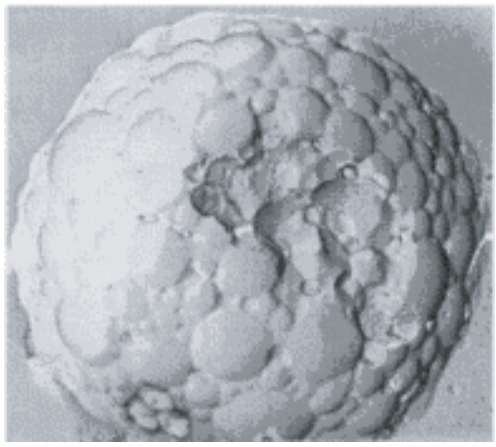

Figure 4. Electron micrograph of multivesicular liposomes (DepoFoam™). Reprinted from YE Q, ASHERMAN J, STEVENSON M, BROWNSON E, KATRE NV: DepoFoam™ technology: a vehicle for controlled delivery of protein and peptide drugs. *J. Control. Release* (2000) **64**(1-3):155-166 [75], Copyright (2000) with permission from Elsevier.

may not be the best candidate for sustained drug delivery via nonvascular routes of administration, simply because of the relatively limited drug-loading capacity and short release duration for the entrapped drugs. This is particularly true when comparing the drug delivery profile of liposomal systems with other solid lipid and polymeric particulate delivery systems. Large-scale manufacturing of liposomes can still be very challenging even with the recent technological advances in aseptic techniques and process controls. Furthermore, optimisation of the long-term physical stability of a liposomal formulation remains a critical task in new product development.

3.2 Multivesicular liposomes

DepoFoam™ (SkyePharma) is a lipid-based drug delivery system consisting of microscopic, spherical particles (10 – 20 µm) composed of hundreds of nonconcentric aqueous chambers encapsulating the dissolved drug to be delivered (Figure 4). The individual chambers are separated by bilayer lipid membranes made up of synthetic phospholipids (i.e., dierucyl phosphatidylcholine and dipalmitoyl phosphatidylglycerol), cholesterol and triglyceride [74]. Due to the similar lamellar structures between DepoFoam and conventional liposomes, DepoFoam systems are also named multivesicular liposomes. Release of the drug from DepoFoam is controlled by its diffusion through the phospholipid bilayers, which undergo phase transition at body temperature [57]. Because of this temperature sensitivity, finished DepoFoam products are refrigerated during long-term storage. The rate of drug release from a DepoFoam formulation can be tailored for a period of 1 day to several weeks by changing the lipid components, composition of the aqueous solution and process parameters used in manufacturing of the formulation [74].

The DepoFoam technology has been successfully applied in the development of several sustained-release products of water-soluble small molecules for nonintravenous administration. DepoCyt® is the first approved DepoFoam product containing cytarabine for the treatment of lymphomatous meningitis via intrathecal injection once every 2 weeks. DepoDur® is a morphine sulfate DepoFoam formulation for 2 days of postsurgical pain relief with one epidural injection. DepoBupivacaine®, an extended-release formulation of a local anaesthetic agent, is currently in Phase I clinical trial [307]. DepoFoam formulations of protein and peptide drugs such as insulin, leuprolide, enkephalin and octreotide have also been developed and characterised for *in vitro* and *in vivo* drug release [75].

3.3 Lipid microparticles

Lipid microparticles are solid lipid-based drug delivery systems with the drug molecules being either dissolved or dispersed in the solid lipid matrix. A lipid microparticle formulation possesses sustained-release properties due to the low mobility of drugs in the solid carrier and the hydrophobic nature of the lipid [76]. The loading efficiency of a drug in lipid microparticles depends on the solubility or miscibility of the drug in the melted lipid, and the chemical and physical properties of the solid lipid. A maximum loading capacity of 25% has been reported [77].

Lipid microparticles were prepared and evaluated for the sustained release of small molecules, such as local anaesthetics [78] and antibiotics [79] as well as proteins and peptides [80,81]. Different methods have been developed to prepare lipid microparticles. Drug molecules can be encapsulated in the lipid matrix by solvent-evaporation method, melt-dispersion method or spray-congealing method [82]. Most recently, lipid microspheres prepared by using a solvent-free coating process based on supercritical fluid technology has also been reported [83]. Depending on the method of fabrication, lipid microparticles can be in the form of a fluid dispersion or a dry powder for reconstitution. Phospholipids are commonly used as a stabiliser in suspension formulations of lipid microparticles (lipospheres). The use of synthetic phospholipids has shown to yield dispersions of bupivacaine lipospheres with enhanced long-term physical stability [84]. The formation of metastable forms of triglycerides during the melt–resolidification process and their subsequent polymorphic transformation have been shown with bupivacaine tristearin microparticles prepared by a spray congealing process [78].

3.4 Cochleates

Cochleates are a lipid-based drug delivery system that is formed by the condensation of small unilamellar negatively charged liposome composed of an anionic phospholipid such as phosphatidylserine. In the presence of a cation (i.e., calcium), the small liposomes fuse to form larger lipid bilayer

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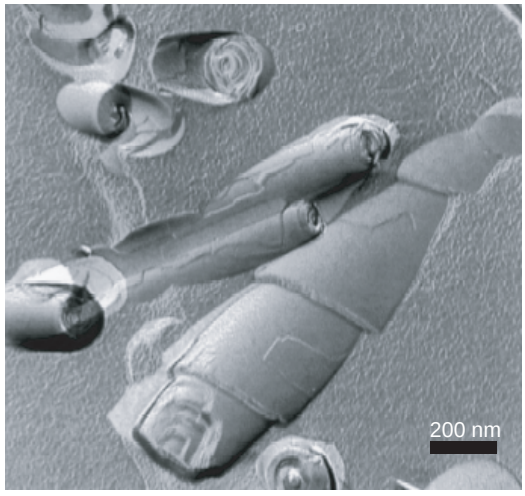

Figure 5. Transmission electron micrograph after freeze fracture of cochleate cylinders. Reprinted from ZARIF L: Elongated supramolecular assemblies in drug delivery. *J. Control. Release* (2002) **81**:7-23 [144], Copyright (2002) with permission from Elsevier.

sheets that subsequently roll up into a cigar-like structure to minimise the interactions between the hydrophobic surface of the sheets and water (Figure 5). Cochleates are cylindrical in shape and their structures are characterised by the tightly packed bilayers with little or no internal aqueous space [85]. Hydrophobic drugs, amphiphilic drugs and molecules with pH-induced charges can be entrapped in cochleates. A hydrophobic or amphiphilic drug molecule is primarily embedded into the lipid bilayers, whereas molecules with pH-induced charges can be easily encapsulated between the bilayers [86]. The unique compact structure of cochleates provides good protection for entrapped molecules from harsh environmental conditions or enzymatic degradation such as in the gastrointestinal tract [87].

Cochleate technology has been used initially to develop an oral formulation of amphotericin B (Bioral™ amphotericin B, BioDelivery Sciences International) for antifungal treatment. In preclinical studies, amphotericin B cochleates exhibited comparative antifungal activity, but with reduced toxicity as compared with injectable forms of amphotericin B [88]. The nano size range (~ 500 nm) and the bilayer lipid structure of cochleates are the desirable characteristics of an intravenous sustained-release drug delivery system. The intravenous administration of amphotericin B cochleates to mice resulted in a blood circulation time longer than that reported for a liposomal formulation of the drug. The unique ability of cochleates to penetrate and accumulate in target tissues was attributed to the ability of cochleates to maintain the structural integrity in blood [89]. Recently, cochleates have further been evaluated as the delivery system for vaccines [90,91] and genes [92].

4. *In situ* depot-forming systems

In situ depot-forming systems for sustained parenteral drug delivery are liquids or semisolids with a wide range of viscosities. Such systems usually contain a biodegradable carrier dissolved or dispersed in a solvent/cosolvent system, whereas the drug is either dispersed or dissolved in the liquid phase of the delivery system. Following subcutaneous or intramuscular injection, a solid depot is formed at the site of injection. The administration of such a system is far less invasive and costly than the surgical procedures required for implantation. The preparation of most injectable *in situ* depot-forming systems mainly involves a relatively simple solid–liquid dispersion or dissolution step. The product is manufactured primarily aseptically, although γ-irradiation can be a feasible means for terminal sterilisation of the product. If the drug is unstable when irradiated, the liquid phase with the carrier alone can be γ-irradiated separately. In this case, the liquid component is packaged as a separate unit without the drug and mixing is required prior to administration to ensure proper dispersion of the solid drug in the liquid phase. This may not be a straightforward procedure if the viscosity of the liquid is high. Different *in situ* depot-forming systems have been reviewed recently and classified into different categories according to the depot-forming mechanism [93-95].

4.1 *In situ* precipitation systems

The liquid vehicle is composed of a water-insoluble biodegradable carrier dissolved in an organic solvent miscible or partially miscible with water. The drug is either dissolved or dispersed in the liquid to form a solution or a suspension. Following injection, the organic solvent dissipates and water diffuses into the organic phase causing phase separation and precipitation of the carrier, leading to the formation of a depot at the site of injection. The drug release from such a system is generally characterised by a relatively high initial burst, which is largely dependent on the hydrophobicity and concentration of the carrier, the polar nature/water miscibility of the organic solvent and the aqueous solubility and loading of the drug. The drug release subsequent to the initial burst is controlled by the degradation/erosion rate of the carrier.

In situ precipitation systems formed with PLGA copolymers have gained the most attention in recent years because of the regulatory approval of four products (Eligard®, Sanofi-Synthélabo) using the Atrigel® technology for long-term (1 – 6 months) delivery of leuprolide acetate by Atrix Lab (now QLT) [96,308]. *N*-methyl-2-pyrrolidone is the organic solvent used in these marketed products. Other organic solvents such as propylene glycol, dimethyl sulfoxide, tetrahydrofuran, triacetin and ethyl benzoate have also been evaluated for their impact on the initial drug burst. The biocompatibility and systemic toxicity of these organic solvents have been the major concerns. *In situ* depot-forming systems of PLGA have also been developed by Alza Corp. with the use of more lipophilic solvents such as benzyl

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benzoate (Alzamer®), which are claimed to be less irritating and with reduced initial drug burst [203].

The SABER® system (Durect) consists of sucrose acetate isobutyrate dissolved in ethanol, benzyl alcohol or other water-miscible solvents. Owing to the low solution viscosity, the ease of administration with small gauge needles is an obvious advantage over the PLGA systems. A long-acting formulation of SABER–bupivacaine has been in clinical trials for post surgical pain management [311]. The potential application of the SABER system for delivery of peptides and proteins has also been demonstrated by the 7-day sustained release of rhGH in rats from a SABER suspension containing insoluble rhGH powder and PLGA dissolved in the liquid phase as a release modifier [97].

4.2 Thermally induced gelling systems

Thermosensitive biodegradable triblock copolymers have been developed by MacroMed as sustained-release systems for parenteral drug delivery. The copolymer is composed of hydrophobic PLGA blocks (A) and hydrophilic PEG blocks (B) with two distinct block configurations: ABA and BAB. ReGel® is an ABA-type triblock copolymer, which is soluble in water. An aqueous solution of ReGel is a free-flowing liquid at ambient temperature that transforms into a gel at body temperature when injected. The drug release rate is adjustable by changing the hydrophobic/hydrophilic content, polymer concentration, molecular weight and polydispersity of the triblock copolymer [98]. Drugs can be dissolved, suspended or emulsified in ReGel. OncoGel® is a product with paclitaxel incorporated into ReGel for local treatment of solid tumours. Paclitaxel is solubilised and entrapped within the hydrophobic domain of the gel and its release is sustained for 6 weeks as the gel undergoes degradation/erosion. This product is currently in Phase II clinical trials for the treatment of oesophageal cancer [309]. The perivascular sustained delivery of paclitaxel in ReGel has also shown to effectively inhibit neointimal hyperplasia in vascular grafts in dogs [99]. Because of the aqueous nature of ReGel, prolonged sustained release (> 1 month) for a water-soluble drug may be difficult to achieve and a high initial burst cannot be avoided. However, the completely water-based ReGel system has shown promise for protein delivery. A total of 2 weeks of constant release of insulin from a ReGel depot formulation was demonstrated in rats, and an injectable depot formulation of hGH has been under early clinical development by MacroMed [100].

Chitosan is a biocompatible and biodegradable pH-dependent cationic polymer. Chemically, chitosan is an amino–polysaccharide obtained by alkaline deacetylation of chitin, which is a natural component of shrimp or crab shells. A novel injectable *in situ* gelling thermosensitive system has been developed by combining chitosan and an anionic polyphosphate salt, glycerophosphate (GP) [101]. The potential of this system for sustained parenteral drug delivery has been evaluated through a study designed to determine the toxicity and drug-release profile of camptothecin. The drug was homogeneously dispersed in a chitosan–GP system and injected intratumourally into a subcutaneous mouse tumour model. Results from this study showed no evidence of toxicity to the animals and zero-order drug release was achieved in the first 4 weeks after a 5% initial burst in the first day [102].

Poloxamer® 407 is an ABA triblock copolymer that consists of polyoxyethylene and polyoxypropylene units. It is a water-soluble nonionic surfactant that forms an aqueous solution with reverse-thermal gelation properties. A solution with > 20% of the polymer exhibits a low viscosity at low temperatures, but rapidly forms a rigid semisolid gel network at body temperature [103]. This system is likely to be more compatible with proteins because no organic solvent is used; however, the parenteral application of Poloxamer has been limited by its lack of biodegradability and concerns of cytotoxicity at high polymer concentration. An increase in plasma cholesterol and triglycerol levels in rats after intraperitoneal injection of the polymer can be problematic [104].

4.3 *In situ* crosslinked systems

The preparation of a new PEG-based copolymer containing multiple thio (-SH) groups along the polymer backbone has been reported [105]. When an aqueous solution of this copolymer was mixed with a crosslinking agent, α,ω-divinylsulfone-PEG (2 kDa) dissolved in a neutral phosphate buffer, a hydrogel was formed. A water-soluble drug can be dissolved in either solution and it becomes physically entrapped when the hydrogel is formed. Because no organic solvent is used and the crosslinking reaction takes place at ambient temperature in a neutral pH environment, this system is particularly suitable for the delivery of protein drugs. Sustained-release formulations of erythropoietin and other proteins were prepared with this novel copolymer. *In vivo* release of these proteins in rabbits was sustained for 2 – 4 weeks and prolonged biological activity of the released proteins was also demonstrated in the tested animals. Preliminary biocompatibility evaluation in rats and rabbits indicated mild adverse tissue reactions to the *in situ* crosslinked gels.

GelSite® (DelSite Biotechnologies) polymer is a natural acidic polysaccharide that is extracted and purified from the aloe plant. The polymer, in an aqueous solution, forms a gel in the presence of calcium when injected subcutaneously or intramuscularly, thus entrapping a water-soluble drug (i.e., a protein) in the solution and providing for sustained release [204]. In addition to its *in vivo* gel-forming properties, this polymer has shown to specifically bind to and stabilise heparin-binding proteins such as fibroblast growth factor and vascular endothelial growth factor. This binding provides additional control on the drug release without interfering with the biological functions of the proteins [205].

Novel biodegradable comb-branched polymers consisting of amine-modified polyvinyl alcohol backbone grafted with PLGA side chains have been prepared [106]. Nanoparticles of the polymer can be formed by a solvent displacement method. The highly positive charged surface imparts a positive

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zeta-potential to the nanoparticles and provides the binding site for anionic drugs. When a colloidal dispersion of the drug-loaded nanoparticles is injected, a hydrogel will be formed in the presence of ions in the body fluids. This *in situ* hydrogel formation would allow the loading of additional drug in the depot. The drug release from such a system is controlled by the degradation of the polymer and the electrostatic interactions between the drug and the polymer. Preliminary *in vitro* release data for an insulin-loaded system showed ~ 4% of encapsulated insulin/day for at least 4 days after an initial burst resulted from free insulin in the system [107].

4.4 Thermoplastic semisolids

Biochronomer is a new class of POE developed by AP Pharma. The use of highly flexible diols allows the preparation of POEs, which are semisolids at room temperature. Semisolid POEs with a molecular weight ≤ ~ 5 kDa are suitable for injection. A drug can be readily incorporated into the semisolid polymer by mixing at low or ambient temperature and without the use of organic solvents. These mild processing conditions are particularly favourable with respect to proteins. The semisolid formulation is mixed with ~ 20% of monomethoxy polyethylene glycol with a molecular weight of 550 kDa to improve injectability. Because of the hydrophobic nature of POEs, drug released from the depot is controlled by the surface erosion of the polymer [108]. Two products are currently under clinical development: 3% mepivacaine formulation in Phase II clinical trial for postoperative pain management and a formulation containing granisetron for control of chemotherapy-induced nausea [310].

5. Implantable systems

Minor surgical procedures are required to insert an implantable system subcutaneously for systemic therapeutic effects or to place the system into specific body sites for localised treatments. A second surgical procedure for removal of the implant is also necessary if nonbiodegradable implants are used. In spite of the complex and invasive nature of the administration mode, implants are valuable sustained-release parenteral drug delivery systems because of the relatively less restrictive size of an implant (drug dose) when compared with subcutaneous or intramuscular injection volume. The surgical retrievable feature of an implant is a major advantage if early termination of the treatment is warranted in case of adverse events. This feature is particularly desirable for some specific medical applications such as long-term treatment for female contraception. Unlike the microparticulate systems, the use of nonbiodegradable carriers in the fabrication of implants is also possible, as the implant can be removed following the completion of the treatment. Drug release from biodegradable implants is mainly controlled by matrix erosion or membrane diffusion, whereas other release mechanisms such as osmotic pressure control can be applied to nonbiodegradable implants.

5.1 Biodegradable implants

Gliadel® Wafer (Guilford Pharmaceuticals) is a polyanhydride implant containing carmustine and approved for the treatment of recurrent glioblastoma multiforme. The copolymer is composed of 1,3-*bis*(*p*-carboxypenoxy) propane and sebacic acid (p[CPP:SA]) in a 20- to 80-molar ratio. The implant is prepared by spray drying a dichloromethane solution of p(CPP:SA) and carmustine to form microspheres, which are subsequently compressed to form wafers with a dimension of 14.5 mm in diameter and 1 mm in thickness [109]. It is designed to deliver carmustine directly into the surgical cavity at the time of surgery. Gliadel Wafer has been shown to release carmustine *in vivo* over a period of 5 days and the copolymer completely degraded over a period of 6 – 8 weeks when in continuous contact with interstitial fluid [2].

A polyanhydride implant containing gentamicin sulfate was developed for sustained local delivery of the drug to the site of infection for the treatment of osteomyelitis [3]. The copolymer is composed of SA and erucic acid dimer in a 1:1 weight ratio. The implant, in the form of a strand of five beads (12 mm long and 4 mm in diameter) with linkers, was prepared by an injection moulding process. Excellent efficacy results were demonstrated in different animal infection models. Results from a Phase II clinical study also showed high local drug concentrations at the implantation sites whereas systemic exposure to the drug remained very low. Polyanhydride copolymers undergo degradation/depolymerisation even at refrigerated temperatures; hence, subzero temperatures (i.e., -20°C) are required for long-term storage of the finished product.

Biodegradable glyceryl monostearate implants containing cefazolin and vancomycin were fabricated and evaluated for the prevention of postoperative wound infections. The ability of these implants in eradicating infections was demonstrated by the results from *in vivo* studies conducted using a rat infection model. Local delivery of the antibiotics was also shown to provide higher drug concentration at the implantation site, resulting in efficacy comparable or better than that achieved by intramuscular injection [110,111].

Implants composed of biodegradable polymer PLGA have been developed and marketed. Zoladex® (AstraZeneca) is a PLGA implant (1- and 3-month depot) containing goserelin acetate and is approved for the treatment of prostate cancer, endometriosis and uterine fibroids. Durin® is an implant system also based on PLGA and is currently developed by DURECT. It is a reservoir-type implant consisting of a drug-loaded core surrounded by a rate-controlling membrane. The drug-release profile can be tailored for continuous or delayed release under zero-order conditions with low initial burst by controlling drug loading, polymer composition and molecular weight, device geometry, permeability of the membrane, and manufacturing process [206]. The Durin–leuprolide implant is under development by DURECT for the treatment of Alzheimer's disease [311].

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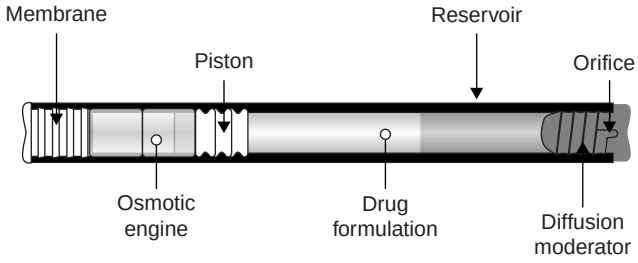

Figure 6. Cross-sectional diagram of the Duros® implant. Reprinted from WRIGHT JC, LEONARD ST, STEVENSON CL *et al.*: An *in vivo/in vitro* comparison with a leuprolide osmotic implant for the treatment of prostate cancer. *J. Control. Release* (2001) **75**(1-2):1-10 [115], Copyright (2001) with permission from Elsevier.

5.2 Nonbiodegradable implants

Norplant® (Wyeth) is a 5-year contraceptive implant approved by the FDA for use by women in the US. The Norplant system consists of a set of six flexible closed capsules made of silicone rubber tubing (silastic) of 2.4 mm in diameter and 34 mm in length. The Norplant implant is a reservoir system with each capsule containing levonorgesterol 36 mg crystals encapsulated inside the silicone membrane [112]. The Norplant implant has been shown to provide effective sustained release of levonorgesterol for up to 5 years. Due to adverse events and problems with its removal, the supply of Norplant was discontinued [312]. Jadelle® (Wyeth) was designed to achieve the same performance of Norplant with fewer units (two rods) to simplify insertion and removal [112]. This product has been formally approved by the FDA, but so far has not been marketed. Implanon® (Organon) is a single-rod implant (40 mm in length and 2 mm in diameter) containing etonogestrel microcrystals (67 mg) embedded in an ethyl vinyl acetate (EVA) matrix, which is encapsulated by a thin rate-controlling EVA membrane [112]. This 3-year contraceptive implant product was granted market approval by the FDA in late 2004. EVA was also used to prepare implants of Nalmefene, an opioid antagonist for the treatment of alcoholism, and the results of an *in vivo* implantation study in rats showed that the implants produced 6 months of stable drug levels with dose proportionality, but no adverse effects [113].

Duros® (DURECT) is an implant system designed for long-term delivery of potent therapeutic agents via a drug-release mechanism driven by osmotic pressure. The implant consists of a titanium alloy outer cylinder, an osmotic engine, a piston and a drug chamber (Figure 6). The outer cylinder is capped at one end with a semipermeable rate-controlling membrane and at the other end with a diffusion moderator containing an orifice through which the drug is released. The dimension of the Duros implant can be 4 mm in diameter by 44 mm in length or smaller and the volume of the drug reservoir is < 200 µl. In operation, water diffuses through the membrane due to the osmotic gradient between the osmotic engine containing sodium chloride (osmotic agent) and the extracellular fluid. In response to the influx of water, the osmotic engine expands, displacing the piston and contracting the volume of the chamber containing the drug formulation. The drug is delivered through the exit port at a precisely controlled rate corresponding to the rate of water permeation into the osmotic engine [114].

Excellent *in vitro* and *in vivo* correlation has been demonstrated for the release of leuprolide from a Duros implant in both animal studies and human clinical trials [115]. A formulation with a high drug concentration may be required to provide the total drug dose required for long-term delivery. Various aqueous and nonaqueous solvents have been evaluated for use in the Duros system [116]. Stable nonaqueous suspension formulations of peptide and proteins have also been reported [117]. Viadur® (Alza Corp.), a 1-year leuprolide acetate implant, is the first Duros system to receive FDA approval for the palliative treatment of advanced prostate cancer [118]. Chronogesic®, a 3-month sufentanil implant, is under development by DURECT for chronic pain management. The system is able to deliver sufentanil at a zero-order rate for > 90 days [119]. In addition, site-specific Duros drug delivery systems for intratumoural delivery of antineoplastic agents into the brainstem and intrathecal delivery of opioid for chronic pain have also been reported [116].

Hydron® implant (Valera) is a hydrogel reservoir drug delivery system designed for sustained parenteral delivery of drugs at a predetermined rate over a 12-month period. The implant is a cylindrical capsule prepared by a spin casting technology and is 26 mm long, 3.5 mm in diameter and 0.5 mm in wall thickness. Chemically, the implant is composed of a crosslinked copolymer of hydroxypropyl methacrylate and 2-hydroxyl methacrylate. It is filled with the solid drug and sealed. Vantas® (Valera), a 12-month histrelin implant, is the first Hydron implant product that has recently been approved by the FDA for the treatment of metastatic prostate cancer. The drug core inside the capsule contains histrelin acetate (50 mg) and stearic acid [120]. The implant is packaged in a glass vial containing 1.8% sodium chloride solution. The soaking of the implant in the sodium chloride solution allows the hydration of the polymer wall and the dissolution of the drug inside the drug core priming the implant for release of the drug on implant insertion. When comparing with implants made of metals, the more flexible nature of the hydrogel implants may cause less discomfort in patients wearing them for long-term treatment.

6. Chemical conjugation

The prolongation of blood circulation time of biologically active molecules by covalently linking them to a hydrophilic polymer has been proven to be a successful approach in protecting these molecules from proteolysis by blood enzymes and clearance by the kidney via filtration. Synthetic and natural polymers that have been evaluated

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for their ability to extend the circulation half-life of biologically active molecules include PEG [121], polysialic acid [122], polyacetals [207], dextrin [208] and albumin [209]. Because of the solution nature of these systems, the final product can be administered intravenously.

6.1 Pegylation

Pegylation is a conjugation process involving the linkage of PEG to a protein molecule. As a result of PEG conjugation, the molecular size of the drug increases and the molecular surface is masked with the hydrophilic chains of PEG, thus reducing kidney filtration, enzyme proteolysis, immune system recognition and phagocytosis by the reticulo–endothelial system [123]. Improved pharmacokinetic profiles by pegylation have been reported for different types of biopharmaceuticals such as cytokines (IL-6, TNF-α, IFN-α) [124-126], erythropoietin [127], growth hormone-releasing factor (GRF) [128] and antibody fragments [129]. Several pegylated IFNs (PEG-IFN-α_{2a} and PEG-IFN-α_{2b}) have been launched and have become successful marketed products for the treatment of chronic hepatitis C in recent years. More pegylated proteins are in different phases of clinical trials [313].

When carrying out the conjugation reaction, PEG is first activated by converting the hydroxyl end groups to a functional group capable of reacting with the lysine or N-terminal amino groups of the protein. The chemistry of pegylation has been extensively reviewed [130,131]. Initially, pegylation was restricted to the use of low molecular weight methoxy–PEGs (< 12,000 Da) due to diol contamination in the reagents. Weak linkages are formed with the difunctional reagents and the conjugation is complicated by side reactions. Purification and the removal of diol contaminants from pegylation reagents allow the use of high molecular weight PEGs (> 20,000 Da) to form conjugated products with much increased circulation half-life as demonstrated by pegylated IFN-α [126].

Site-specific mutagenesis is another approach used to attach PEG to the predetermined sites of a protein molecule. Pegylated recombinant staphylokinase (Sak) was prepared by site-directed substitution with cysteine followed by derivatisation with linear PEG molecules containing thiol-specific functional groups. PEG–Sak has been evaluated for the treatment of patients with ST-segment elevation acute myocardial infractions. Preliminary pilot studies have shown that the conjugate was an effective bolus agent for acute myocardial infraction, but significant adverse events and mortality were reported in a clinical trial [132].

6.2 Polysialylation

PolyXen® (LipoXen) technology is based on the use of *Escherichia coli*-derived α-(2-8)-linked polysialic acids (PSA) with average molecular weights of 22 and 39 kDa. PSA is biodegradable and the degradation product sialic acid is known to be nontoxic [133]. A drug is conjugated to PSA via covalent bonds. The increase in circulation half-life is dependent on the chain length of PSA. A longer chain of PSA results in longer circulation time of the conjugated molecules; half-lifes of up to 40 h were shown in mice [134]. Results from preclinical studies have shown that long circulating PSA–drug conjugates also retained bioactivities [135,136]. Asparaginase conjugated to PSA exhibited resistance to proteolysis with 65 – 83% of the initial enzyme activity remaining after 6 h of exposure to mouse blood at 37°C, whereas most of the native enzyme was inactivated under the same conditions. *In vivo* experiments using mice revealed that the half-life of polysialylated asparaginase given intravenously was significantly extended as compared with the native enzyme [135].

SuliXen® (LipoXen) is a polysialylated insulin developed for the treatment of Type 2 diabetes. The polysialylated insulin was shown to reduce the blood glucose concentration to the same level as that achieved by subcutaneous injection to mice within the same time period. This result demonstrates that polysialylation did not hinder the interaction of insulin with its receptor. An 80-fold increase in the half-life of a polysialylated tumour-specific Fab fragment was observed in rats. The improved localisation of the Fab in the relevant tumour attributable to prolonged circulation time suggested that the antigen-recognising region in the Fab was not negatively affected by the polysialyation. The Fab was able to approach and bind to the relevant antigen on the cell surface [137]. Polysialic erythropoietin for chronic anaemia and polysialic IFN-α_{2b} for hepatitis C are being evaluated in the preclinical stage [314].

6.3 Drug affinity complex

Drug affinity complex (DAC®, ConjuChem) is formed by conjugating a therapeutic agent with an endogenous protein such as albumin *in vivo* [209]. Each DAC construct is composed of three components: a peptide or a small molecule drug, a connector covalently attached to the drug and a reactive functional group at the opposite end of the connector for the covalent bonding of the construct to a target protein in the body. The DAC construct can be administered to the patients by intravenous or subcutaneous injection. The reactive portion of the DAC construct will then covalently bond to a single known site on albumin. The therapeutic agent maintains its original biological activity while adopting the distribution, metabolism and excretion profile of albumin.

DAC technology is applicable to small organic compounds, peptides and radiotherapeutic compounds. A DAC–glycagon-like peptide-1 (GLP-1) is a GLP-1 derivative with a short covalently reactive chemical linker that interacts with a specific cysteine residue in albumin following parenteral administration [138]. DAC–GLP-1 is currently in Phase II clinical trial for the treatment of Type 2 diabetes [139]. Another product under development is DAC–GRF for the treatment of growth hormone disorder. Phase I clinical trial results showed that this compound was safe and well tolerated; more importantly, it exhibited excellent biological response to growth hormone and IGF-1 levels. The IGF-1 levels were sustained within the therapeutic target range for > 21 days subsequent to the first injection [315].

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6.4 Polyacetal–drug conjugates

Fleximer® (Nanopharma) is a family of highly hydrophilic polyacetals with molecular weights in the range of 2 – 1000 kDa. Fleximer polymers are biocompatible and biodegradable. The polymers that are not recognised by the immune system can circulate in the blood for several hours to 1 day. The blood circulating time of the polymers can be modified by changing the length of the backbone. The backbone can also be tailored to produce different conjugates of the drug molecule targeting to multiple binding sites. Fleximer polymers are readily conjugated with proteins, peptides and small molecules via the terminal and pendant functional groups [207].

6.5 Dextrin-based polymers

Dextrins are α-1,4-polyglucose polymers obtained by enzymatic hydrolysis of corn starch and have been evaluated as drug carriers to improve the pharmacokinetic profile of drugs. Dextrin–drug conjugates have been prepared by reacting succinoylated dextrin with drugs [208]. Dextrins are readily degraded by plasma α-amylase and the rate of degradation is highly dependent on the degree of dextrin backbone substitution. A dextrin–doxorubicin conjugate prepared from succinoylated intermediates exhibited slow degradation over 7 days in an *in vitro* study [140].

7. Expert opinion and conclusion

In view of the vastly diversified natures and markedly different delivery mechanisms of various sustained-release systems available for parenteral drug delivery, a thorough understanding of the design requirements for the drug product and the characteristics of the delivery system is crucial while searching for the best match. The key factors to be considered are drug or delivery system specific and it is important to realise the close interdependent relationship between these two groups of factors. Drug-related factors include therapeutic requirements, pharmacokinetic parameters and physicochemical properties. The product design criteria for a delivery system are different for systemic or localised treatment. Biodegradable nanosystems and chemically conjugated water-soluble systems can be given via the intravenous route for systemic effects, whereas the subcutaneous and intramuscular routes are suitable for implants, *in situ* depot-forming systems and biodegradable microparticulate systems. Due to the volume constraints on subcutaneous and intramuscular injection (≤ 1 ml), implants for subcutaneous insertion can be a more feasible option when the delivery of a larger dose is required, particularly for long-term treatments. When localised delivery is the treatment goal, the size and physical form of the delivery system as well as the mode of administration should be compatible with the site of application. Localised injection of a microparticulate system can be a convenient technique and the placement of an implant in a body cavity has been a common practice.

The daily dose of a drug can be estimated by knowing the biological half-life and the therapeutic level of the drug. With the known daily dose and desirable sustained-release duration, the total drug dose is calculated. Different delivery systems vary considerably in their drug-loading capacities, which are largely dependent on the physical features and controlled-release mechanism of the system. The final drug dose delivered by a microparticulate system is much less than the actual drug loading of the system because of the need for reconstitution with a liquid medium prior to administration. In comparison, an implant and an *in situ* depot-forming system can provide a higher drug loading capacity with a specific release rate, as the surface area for drug release of these systems is relatively low. Unlike the delivery systems for subcutaneous or intramuscular injection, the less restriction on the size of an implant may also offer a distinct advantage in delivering a larger drug dose.

The physicochemical properties of the drug have a significant influence on the design of a delivery system. Drugs with high water solubility pose a bigger challenge to be incorporated in delivery systems composed of hydrophobic carriers. Although these drugs can be formulated with delivery systems providing an aqueous encapsulation or entrapment environment, such as liposomal and hydrogel formulations, these systems have limited loading capacity and exhibit high initial burst release. Lipophilic drugs can be incorporated into hydrophobic carriers, such as solid lipid and polymeric systems. By virtue of the low aqueous solubility, a high drug loading is easier to achieve with a lipophilic drug. The chemical compatibility between the drug and the carrier is another important factor to be evaluated. The chemical reactivity of the drug and the carrier is the determining factor for their stability during manufacturing and storage. It is also imperative to evaluate the impact of the processing conditions and the use of processing media (e.g., organic solvents) during manufacture on the stability of the drug. In some instances, stringent packaging requirements, such as a low storage temperature and moisture resistance, are to be employed to ensure the shelf life of the product.

Important aspects of the delivery system worth consideration are the drug-release mechanism, the safety profile, the manufacture complexity, regulatory history and patent protection. If the controlled drug-release mechanism of a delivery system is well defined and the key formulation variables are known, formulation development with a new drug can be implemented with a better chance of success. The drug release characteristics of a sustained-release system are mostly dependent on the controlled-release mechanism, although interaction of the carrier with the drug and the tissue components of the *in vivo* surroundings may also play a role, particularly for long-term release systems. The impact of initial burst release and release kinetics of the delivery system on the safety and therapeutic efficacy of the drug should be carefully evaluated during the product design phase. Attempts to minimise the initial burst effect have not often been successful with biodegradable matrix systems. If a zero-order drug

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release profile is the design goal, reservoir-type systems such as nonbiodegradable implants with a membrane- or osmotic-controlled-release mechanism should be considered. In light of the lack of good *in vitro* to *in vivo* correlation for parenteral sustained-release systems, the performance of a delivery system cannot be predicted based solely on *in vitro* data. Minimally, *in vivo* animal data must be available for technical assessment of the delivery technology. Preclinical and clinical data on systemic toxicity and adverse local tissue responses to the carrier are valuable safety information to be generated during the development phase of the product. The variables affecting *in vivo* degradation of biodegradable carriers should be known so that the degradation rate can be tailored for applications requiring specific degradation kinetics ranging from weeks to months.

The fabrication process of the final product needs to be examined not only with respect to the stability of the drug, but also with the complexities of scale-up and the final manufacturing cost. Because of the sterility requirements, the cost for installing an aseptic process with complex unit operations can be prohibitively high. A high degree of regulatory scrutiny is always applied to a new product, which is the first to be developed with a delivery technology. Therefore, the selection of a delivery system with an approved product in the market can be advantageous, even though each combination of a delivery system and a drug is reviewed and eventually approved on its own merits by the regulatory authority. The patent position of a delivery technology is an important selection criterion. Only a delivery technology with sound patent protection will be used for the development of a commercial product in today's extremely competitive pharmaceutical business world.

In this biotechnology era, proteins that have become the mainstream of modern day therapeutics are predominantly administered parenterally. There is still an unmet need for parenteral sustained-release systems for these drugs. The hydrophilic nature, and the delicate chemical and conformational structures of proteins are the major challenges. The hydrophilic nature of a protein has made it extremely difficult to incorporate the drug in a hydrophobic delivery system. The encapsulation of a water-soluble drug in a hydrophobic carrier system via an emulsion method has proved to be detrimental to some proteins because of the use of organic solvent or high shear energy. In addition to the instability concerns of a protein during fabrication and shelf storage, its stability in the delivery system can be an issue if an adverse microenvironment (i.e., lowering of pH) is created by the biodegradation of the carrier. These technology gaps can only be filled with the advances in delivery technologies constituting the use of novel carriers and fabrication processes that are more compatible and less deleterious to proteins.

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