

Review

Materials for Pharmaceutical Dosage Forms: Molecular Pharmaceutics and Controlled Release Drug Delivery Aspects

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Abstract: Controlled release delivery is available for many routes of administration and offers many advantages (as microparticles and nanoparticles) over immediate release delivery. These advantages include reduced dosing frequency, better therapeutic control, fewer side effects, and, consequently, these dosage forms are well accepted by patients. Advances in polymer material science, particle engineering design, manufacture, and nanotechnology have led the way to the introduction of several marketed controlled release products and several more are in pre-clinical and clinical development.

Keywords: polymers; copolymers; biomaterials; biodegradable; microparticle; nanoparticle; pharmaceutical dosage forms; particle engineering design; manufacture

1. Introduction

Biodegradable and biocompatible materials for pharmaceutical dosage forms have enabled the advancement of pharmaceuticals by providing better therapy and disease state management for patients through controlled release drug delivery, particularly as microparticles and nanoparticles. Controlled release delivery is available for many routes of administration and offers many advantages over immediate release delivery. This review describes controlled drug delivery, the types/classes of biocompatible and biodegradable pharmaceutical polymers, the types of drugs encapsulated in pharmaceutical polymers, microparticle/nanoparticle controlled drug delivery, the particle engineering

design technologies and manufacture of controlled release microparticles/nanoparticles, and currently approved controlled release drug products.

2. Controlled Drug Release Technology of Drugs

In order to achieve efficient disease management, the concentration of released drugs from polymeric matrices should be within the therapeutic window with minimal fluctuation in blood levels over prolonged periods of time at the intended site of action [1–3]. The release of drug can be controlled by diffusion, erosion, osmotic-mediated events or combinations of these mechanisms [4,5]. Typically, a triphasic release pattern is observed, consisting of an initial burst [4], primarily attributed to drug precipitates at the particle surface and surface pores in the polymer, and the osmotic forces in highly water-soluble peptide formulations [6], a lag period depending on the molecular weight and polymer end-capping [5] and finally erosion-accelerated release [6].

Considering release rate control as a key parameter, a decrease in particle size (*i.e.*, an increase in the specific surface area) results in higher release [6]. Also, higher porosity of the particles inducing a larger inner surface can increase the influx of the release medium into the particles and, thereby, facilitate the drug diffusion rate [7]. In addition, the specific properties of the polymer matrix (e.g., the chain length, flexibility and swelling behavior, potential interactions between polymer and drug) will significantly influence the drug release rate [8,9]. Therefore, switching to a different molecular weight or an end group capped polymer, and the use of block copolymers will alter the diffusion and drug release rate [10,11].

To achieve zero-order release kinetics indicative of uniform release with respect to time, which is desired for most applications, a combination of fast- and slow-releasing particles or the use of copolymers are possible alternative advanced methods [12,13]. A one-time only dose can be achieved by co-injection of a bolus of soluble drug as a loading dose and zero-order releasing microspheres as a maintenance dose.

3. Types and Classes of Biodegradable and Biocompatible Pharmaceutical Polymers

Biodegradability and biocompatibility of a polymer are among the most important properties for pharmaceutical applications. Biodegradation is generally described by two steps, namely: (1). water penetrates polymeric matrix, attacking the chemical bonds by hydrolysis and thereby shortening the polymer chain length resulting in a reduction in molecular weight and metabolism of the fragments and bulk erosion; and (2). surface erosion of the polymer occurs when the rate at which the water molecules penetrating the matrix is slower than the rate of conversion of the polymer into water-soluble materials. Biocompatibility refers to specific properties of a material not having toxic or injurious effects on biological systems. Non-biocompatible materials can cause irreversible tissue damage, such as permanent tissue destruction, necrosis, significant fibrosis, and dystrophic calcification.

However, it should be noted that good biocompatibility does not insure good biodegradability. Poly(*N*-isopropyl acrylamide) (NIPAAAM), used to formulate thermo-responsive hydrogels [14], is non-toxic and biocompatible but not biodegradable by hydrolysis. It is of critical importance to investigate both biodegradability and biocompatibility of synthesized copolymers [15,16].

3.1. Polyester-Based Synthetic Polymers

Drug delivery systems based on biodegradable aliphatic polyesters have advanced remarkably over the past few decades. Commonly used polymers (Figure 1 and Table 1) such as poly (ϵ -caprolactone) (PCL), poly (lactide acid) (PLA), and poly (lactic-co-glycolic acid) (PLGA) are FDA-approved and well known for their biodegradability, biocompatibility and non-toxic properties which makes them suitable as matrices for controlled release drug delivery systems. Poly (lactic-co-glycolic acid) (PLGA) has become one of the most studied diblock copolymer biomaterials for drug encapsulation and is present in several commercially available pharmaceutical products. Due to the slow degradation and drug release rates, poly (lactide acid) (PLA) homopolymer has no longer been broadly used for the past two decades. PLGA heteropolymer degrades relatively faster than PLA and can achieve 2–6 weeks release criteria, while PLA delivers drugs over months [7].

Degradation rate of PLGA is attributed to its molecular weight, its distribution, the lactide/glycolide ratio, the polymer end-group, micro/nano particle size, pH, and the temperature of the release medium. Generally, low molecular weight of PLGA degrades faster and as a result it causes more rapid drug release and higher initial burst [17]. The hydrophilicity of PLGA is defined by the lactide:glycolide ratio and affects the release rate in a micro/nano particulate formulation. When the lactide/glycolide ratio increases, the drug release rate decreases [18]. The carboxyl end groups of PLGA are mainly involved in interactions with drug. The initial adsorption of a peptide to hydrophilic PLGA is due to an ionic interaction between the amino group of the peptide and the terminal carboxyl group of PLGA, resulting in initial burst release [10,11]. Also, hydrophilic and acidic properties of free carboxyl groups induce faster water uptake and hydrolysis of ester bonds making more acidic groups by autocatalytic cycle [19]. For particulate drug delivery systems, particle preparation procedure and interactions of polymer with drug, both play important roles in polymer degradation. Higher stirring rate [20] and ultrasound treatment [6] for emulsification can reduce particle size (thereby increasing the surface area per unit volume) of particles resulting in faster degradation upon exposure to the release medium.

In comparison to PLGA, Poly (ϵ -caprolactone) (PCL) has high permeability to small drug molecules and a slow degradation rate which make it suitable for extended long-term delivery over a period of more than a year. While PLGA generates an acidic environment during degradation, which can lead to peptide/protein instability, the ability to avoid acidic conditions has become one of major advantages for selecting PCL as a drug carrier [21].

Poly(ethylene glycol) (PEG), also known as polyethylene oxide (PEO), is a largely exploited polymer for advanced physical and chemical stability of drugs and its “stealth” properties. Abuchowski, Davis and co-workers first described a method for the covalent attachment of mPEG to proteins in 1977 [22], which has since been termed PEGylation. PEG is an amphiphilic polymer composed of repeating ethylene oxide subunits and can dissolve in organic solvents as well as in water. Ordinarily, the properties of PEG that are of particular relevance in pharmaceutical applications are: (1). improved circulation time due to evasion for renal or cellular clearance mechanisms; (2). reduced antigenicity and escape from phagocytosis and proteolysis; (3). improved solubility and stability; and (4). reduced dosage frequency, with reduced toxicity [10,23,24]. Degradation rate of PEG depends both on the molecular weight and on the concentration of PEG. The degradation mechanism is

explained by the strong hydrophilicity of PEG, the hydrogen-bonding interaction between PEG and water [23].

Polyvinyl alcohol (PVA), a homopolymer with measurable surface activity, has some similarities with PEG in that it is comprised of a repeating monomer unit that is hydrophilic, as shown in Figure 1. PVA plays a variety of functions in controlled release delivery systems including the following; as a matrix of particle [25], hydrogel [26], and as a surfactant in emulsion systems during formulation processes for micro/nano particles [27–29]. PVA can be grafted with a chain of polymeric substrate [30,31]. For example, in PVA-grafted PLGA polymer, the PVA backbone can be modified to create negatively or positively charged properties using sulfobutyl or amine moieties and the resulting increase in the hydrophilicity of this polymer provides advantages when carrying sensitive biomolecules, such as proteins, peptides and DNA [30].

As shown in Figure 1 and Table 1, poly(*N*-vinylpyrrolidone) (PVP) has been extensively used in controlled release drug delivery due to its biocompatibility, chemical stability, and excellent aqueous solubility [24,32]. Moreover, a polymer matrix combined with PVP has been known to reduce nonspecific protein adsorption [33]. Kollidon[®]SR is a compressible polymeric blend composed of polyvinyl acetate (PVAc) and povidone (PVP) commercially available and used often in pharmaceutical dosage forms [34]. The amorphous nature of PVAc and its low glass temperature (T_g) of 28–31 °C impart unique characteristics to Kollidon[®]SR. By the gradual leaching of water-soluble PVP, the matrix creates channels for releasing drugs [35]. Due to excellent solubility, the soluble grades of Kollidon[®] usually have no delaying effects on the dissolution of drugs and can be used as a hydrophilic component in dosage forms that contain controlled-release excipients, such as cetylalcohol, alginate, cellulose derivatives, polyactic acid, polyvinyl alcohol, ceresine wax, stearic acid or methacrylate copolymers to control the release of drugs, as binders or sometimes as plasticizers [34].

3.2. Natural Origin Polymers Used as Pharmaceutical Excipients

Naturally derived polymers with special focus on polysaccharides and proteins have become attractive in the biological applications of controlled release systems due to their similarities with the extracellular matrix in the human body and favorable specific properties that can be exploited for “smart” systems, for example, stimuli-responsiveness. Polysaccharides are a class of biopolymers constituted by either of one or two alternating monosaccharides, which differ in their monosaccharide units in the length of a chain, in the types of the linking units and in the degree of branching [36]. Table 1 lists FDA-approved natural origin polymers and their routes of administration.

Starch, composed of amylose and amylopectin, is generally modified to change its physical properties by adding plasticizers, such as water and glycerol, improving the flexibility of starch which is favorable in pharmaceutical applications [37,38]. In addition, cross-linking techniques can lead to advanced drug delivery systems by compensating for weak points of plasticized starch which is sensitive to moisture, shows low tensile strength and Young’s modulus [39]. Due to its high hydrophilicity, starch has bioadhesive properties [8] that are favorable for ophthalmologic drug delivery (*i.e.*, timolol, flurbiprofen) [40].

Chitosan is a polyaminosaccharide, prepared by the N-deacetylation of chitin. Chitosan is thermo-stable due to its strong intramolecular hydrogen bonding between hydroxyl and amino groups. As a weak poly-base, reversible pH-sensitive behavior, due to its large quantities of amino groups on its chain, makes chitosan applicable in hydrogel smart delivery systems. Chitosan is soluble in water and in organic acids such as formic, tartaric, acetic, and citric at low pH (<pH 6.5) due to protonation of the amino groups [41]. For particulate drug delivery, a cross-linking technique by glutaraldehyde is generally used [42].

Alginate, a marine-derived polysaccharide, is abundantly available in nature and is an attractive alternative for controlled release systems, as it is amenable to sterilization and storage [43]. Alginate is an anionic block copolymer consisting of β -D-mannuronic acid (M) and α -L-guluronic acid (G).

Table 1. Polymeric inactive ingredients for FDA-approved drug products.

Polymeric inactive ingredients for FDA-approved drug products	
Polyester-based synthetic polymers	PLGA (for IM, SC uses)
	Poloxamer (for oral, topical, IV ophthalmic, SC uses)
	Polyvinylpyrrolidone ethylcellulose (for oral use)
	Sodium pyrrolidone carboxylate (for topical use)
	Povidone (for oral, intra-articular, IM, Intrauterine, topical, SC, respiratory, ophthalmic uses)
	PLA (for IM use)
	PEG (for oral, respiratory, topical, IM, IV, ophthalmic uses)
	PVA (for auricular, IM, intraocular, topical uses)
	KOLLIDON VA 64 (for oral use)
Natural-origin polymers	Starch (for oral, IV, IM, topical)
	Hyaluronate (for intra-articular, IM, intravitreal, topical uses),
	Human albumin (for IV, SC, Oral uses)
	Gelatin (for IM, SC, IV, oral topical uses)
	Alginate (for ophthalmic and oral uses)
Collagen (for topical use)	

Alginate forms a stimuli responsive hydrogel in two different ways. One is via hydrogen bonding at pH levels below 2, which is based on the pKa values for carboxyl acid groups in M (pKa 3.38) and G (pKa 3.65). The other way is via ionic interactions with divalent metal ions. Since, chelating agents such as EDTA or phosphate buffer can easily remove Ca^{2+} ions, Ca^{2+} -responsive-hydrogel systems can be designed [44].

Hyaluronic acid is a major carbohydrate component of the extracellular matrix found in synovial fluids and on cartilage surfaces [45]. Hyaluronic acid, an excellent lubricator and shock absorber, inhibits chondrocytic chondrolysis, thereby improving the lubrication of surfaces and reducing joint pain in osteoarthritis [46]. Hyaluronic acid has been widely studied for drug delivery, especially for transplantation, injection and gene delivery particularly as it is non-immunological [45]. To avoid rapid degradation and clearance, when the hyaluronic acid is used as a carrier, its matrix is utilized with cross-linking using glutaraldehyde [37], carbodiimide [37], or polyethyleneglycol diglycidylether (PEGDG) [46].

Bovine Serum Albumin (BSA), a globular protein, is a naturally biodegradable, nontoxic and non-antigenic biopolymer making it suitable for controlled drug delivery. Typically BSA particles are prepared under mild conditions by coacervation or a desolvation process [47,48] and cross-linked by glutaraldehyde. However, polyethyleneimine (PEI) has been suggested to avoid potential toxicity of glutaraldehyde [49].

Collagen is the major protein component of the extracellular matrix. Twenty seven types of collagens have been identified to date, but collagen type I is the most investigated for pharmaceutical applications [37]. Several factors affect degradability of collagen, for example, structure contraction caused by cell penetration, collagenase, gelatinase and other non-specific proteinases can digest collagen [50]. The versatile properties of collagen (e.g., high mechanical strength, good biocompatibility, low antigenicity, and water uptake properties) have made it one of the most useful biomaterials for tissue engineering using a form of collagen sponge [51] or collagen gel [52].

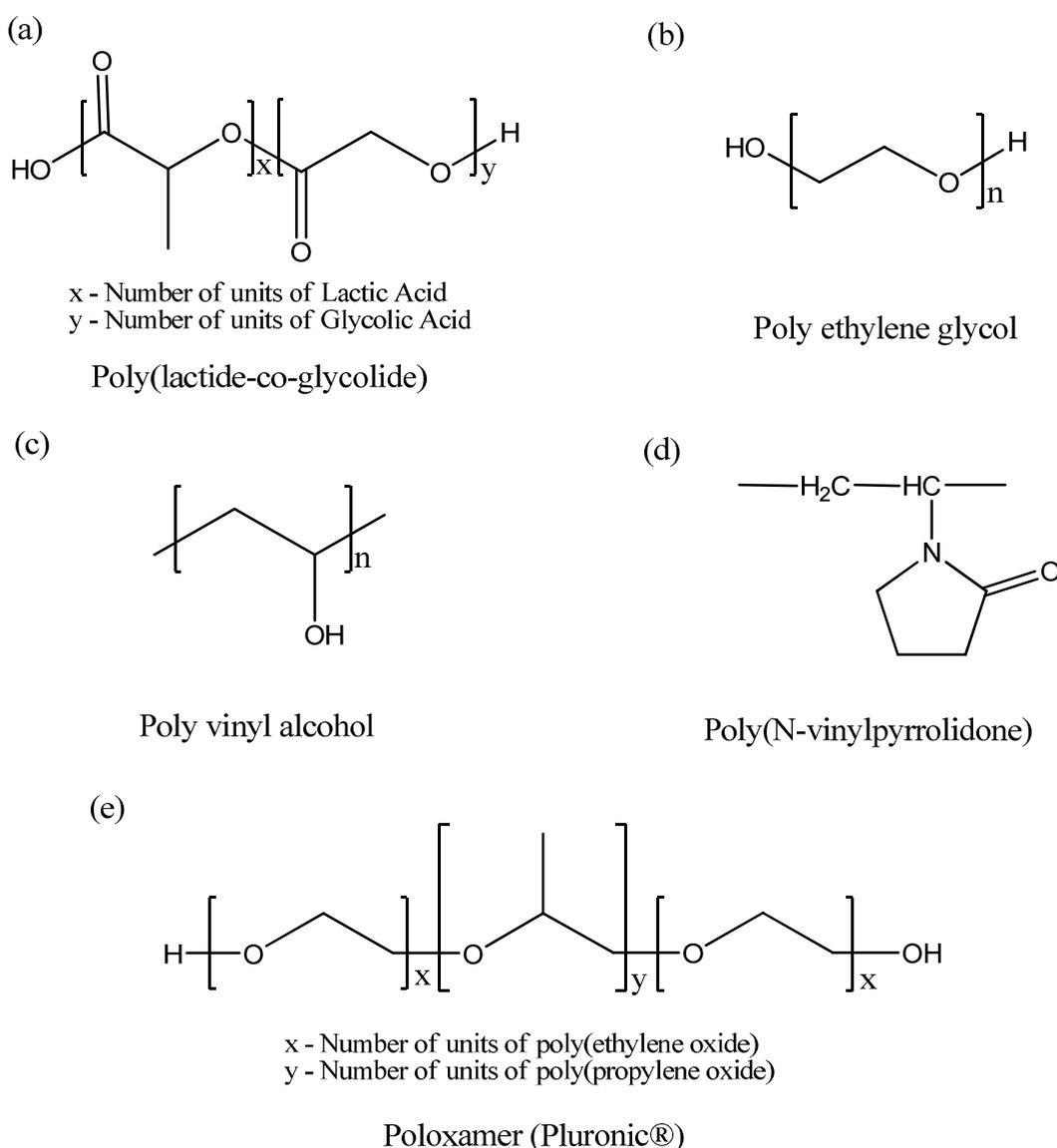
Gelatin is a denatured protein obtained by acid and alkaline processing of collagen [37]. Gelatin, in a variety of isoelectric points, can be manufactured and basic gelatin with an isoelectric point of 9.0 and acidic gelatin with an isoelectric point of 5.0 are mostly used. If the biomolecule to be released is acidic, basic gelatin with an isoelectric point of 9.0 is preferable as a matrix, and *vice versa*. Both gelatins are insoluble in water. To prepare a hydrogel through cross-linking, the gelatin hydrogels forming polyion complexes with proteins will facilitate the release of biologically active proteins [53].

3.3. Homo vs. Diblock Copolymer vs. Triblock Copolymers

To enhance the desirable properties of polymer as a matrix for a controlled drug delivery system, efforts have been made to improve its hydrophilicity, biodegradation rate, and drug stability. The most commonly used hydrophilic block for polymeric drug delivery systems is poly (ethylene oxide)/poly(ethylene glycol), PEO/PEG. PEO is FDA-approved for parenteral administration, due to its low toxicity and biocompatibility [10]. One of the primary advantages of attachment of the PEO moiety is its effectiveness against protein adsorption to hydrophobic surfaces. For polymeric micelles, the length of the PEO blocks affects circulation time and uptake by phagocytes, with longer chains extending circulation time and reducing phagocytosis [54]. As a shell forming material for polymeric micelles, with PEO, PEG (Figure 1) imparts to the micelle with a “stealth character” in the blood compartment, achieving longer circulation [55]. PEG grafted to surfaces of nanospheres proved to reduce thrombogenicity and to increase their dispersion stability in aqueous medium, due to steric repulsion effects of tethered PEG strands [56]. PLGA-PEG-PLGA (ReGel) as controlled release formulations for two weeks delivery of glucagon-like peptide-1 (GLP-1) in type 2 diabetic rats [16]. PEG-PLGA-PEG triblock copolymers with TGF- β 1 have been formulated to accelerate the diabetic wound healing [57]. PVA based branched graft polyester bearing PLGA block, which is first generation, designated as PVA-*graft*-PLGA, shows lower burst effects and controlled release profiles based on the structure and molecular weight of the copolymer [58]. In order to obtain negative charged polymer, as a second generation, branched poly[sulfobutyl-poly(vinyl alcohol)-*g*-(lactide-*co*-glycolide)] (SB-PVA-*g*-PLGA) was reported in which the sulfobutyl groups are covalently conjugated to PVA backbone [59,60]. Third generation, amine-PVA-*g*-PLGA, was developed by attaching various amino groups to the PVA backbone, which is positively charged [61].

Poloxamers, also known by the trade name Pluronic, are nonionic triblock copolymers composed of hydrophilic poly(ethylene oxide) (PEO) and hydrophobic poly(propylene oxide) (PPO) blocks, designated as PEO-PPO-PEO [62]. Due to their amphiphilic characteristics poloxamer exhibits surfactant properties coupled with ability to self-assemble into micelles above critical micelle concentration (CMC) in aqueous solutions. Besides, these copolymers are shown to be potent biological response modifiers capable of overcoming drug resistance in cancer and enhancing drug transport across cellular barriers, such as brain endothelium [63,64].

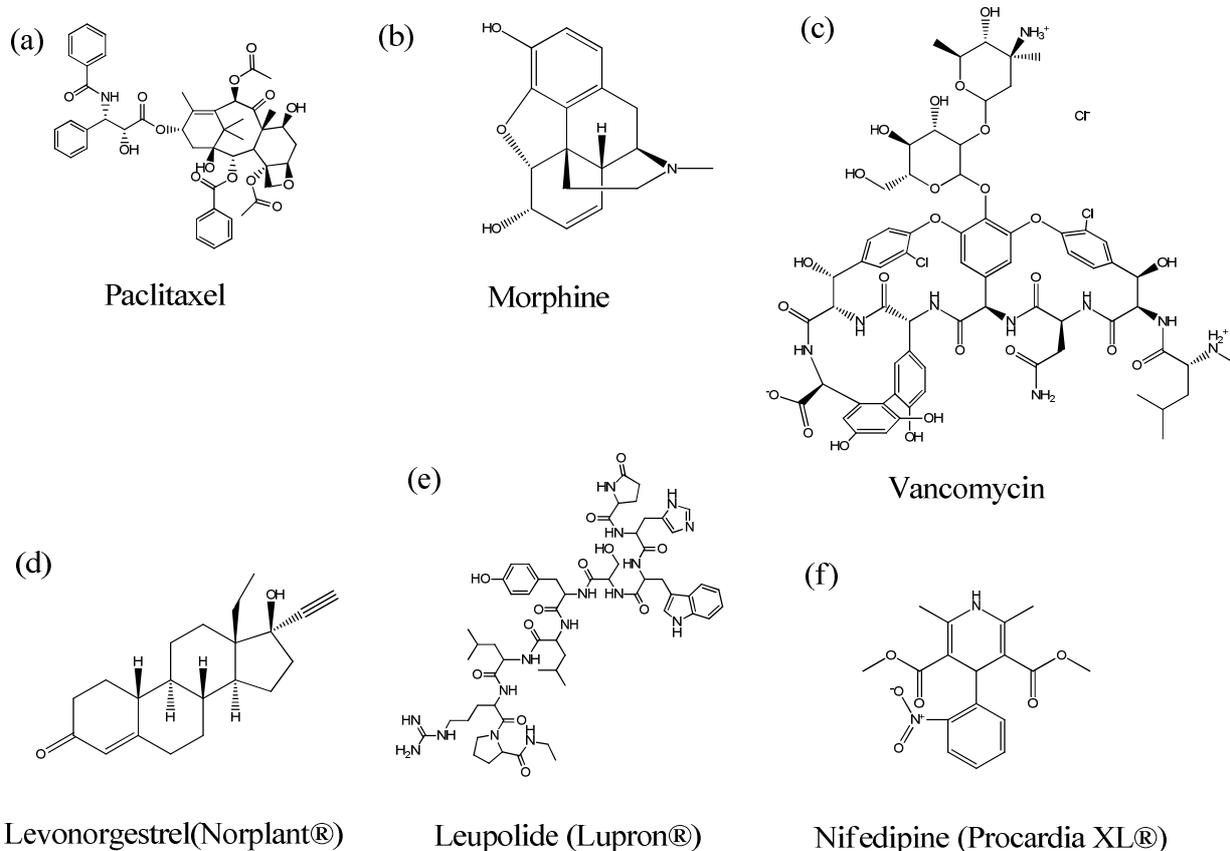
Figure 1. Structures of biodegradable and biocompatible polymers.



4. Therapeutic Agents Encapsulated in Polymeric Particles

Administration of a variety of drugs from different therapeutic classes encapsulated in polymeric particles (Figure 2), particularly through parenteral route, has been extensively investigated to lead to complete absorption of drugs in the systemic circulation and control drug release over a predetermined time span ranging from days to weeks to months.

Figure 2. Various therapeutic agents from different therapeutic classes that have been encapsulated in polymeric particles.



In chemotherapy, obtaining adequate drug levels at the tumor cell is the most primary issue because inadequate tumor cell drug-burden will lead to low cell apoptosis and to early development of drug resistance [65]. Chemotherapeutic agents (Figure 2) such as paclitaxel [66–68], docetaxel [69], vascular endothelial growth factor siRNA [70,71], 5-fluorourasil [72,73], doxorubicin [74,75], adriamycin [76], gancyclovir [77], celecoxib [78,79], bleomycin [80,81], and tamoxifen [29] have been successfully formulated in polymeric particulate delivery systems.

In pain control, opioids (Figure 2) are vital in the treatment of severe and chronic pain associated with cancer and certain chronic diseases. Morphine [82,83], nalbuphine [84], tramadol [85], buprenorphine [86,87], fentanyl [88,89], and hydromorphone [90] have been developed to accomplish prolonged drug release so that patients' compliances, and by extension, quality of life for patients suffering chronic pain can be improved. In addition, non-steroidal anti-inflammatory drugs (NSAIDs) such as flubiprofen [91], ibuprofen [92], celecoxib [93,94], diclofenac [95,96], and indomethacin [97,98], have been developed as encapsulated drug microspheres. Several local anesthetics also have been reported with opioids [90,99]. Lidocaine [100], tetracaine [101], bupivacaine [90], and ropivacaine [102] were studied for drug encapsulated polymeric particulate system.

Antibiotic drug delivery will decrease the bacterial load at the infection site, minimizing renal, liver and systemic toxicities. Application of controlled drug release systems offers advantages in maintaining a highly site specific drug concentration for an extended period while reducing systemic toxicity and drug resistance. Antibiotics (Figure 2) incorporated in controlled release systems include

chlorhexidine [103], vancomycin [104], amphotericin B [105], gentamicin [106,107], and doxycycline [108–110].

Growth hormones and birth control hormones (Figure 2) have been mostly focused for sustained release formulation. Encapsulation of growth hormone in biodegradable PLGA microspheres has been a typical technique to prolong the effect of the drug. Human growth hormone, a somatotropic hormone to treat growth hormone deficiency (GHD), chronic renal insufficiency, Turner's syndrome, and cachexia secondary to AIDS, has been developed to reduce the need for frequent administrations by maintaining *in vivo* drug levels in the therapeutic range [28,111,112]. On the other hand, octreotide, a synthetic anti-somatotropic agent for the treatment of acromegaly and endocrine tumors, has been formulated in PLGA microspheres and commercialized as Sandostatin[®] LAR[®] depot (Novartis Pharma, Basel, Switzerland) on a monthly basis [113]. The use of polymers to deliver birth control hormones has evolved over the years. The first system, Norplant[®], consisted of six levonorgestrel contraceptive implants for a five year duration of use. By replacing the initial model of silastic capsules containing steroid crystals with a solid mixture of the steroid and a polymer (rods) covered by a release-regulating silastic membrane, it was possible to release the same amount of contraceptive steroid delivered by six capsules through two rods, which is a second generation implant system, Jadelle[®] [114]. However, these products are silicone based devices, which are non-biodegradable with considerable long-term toxicities. Consequently, the devices need to be removed after depletion of the drug. To overcome this problem, PLGA microspheres have been studied for implantation using levonorgestrel under the skin without special surgery [115–118].

Patient compliance rates are notoriously poor in antipsychotic medications due to the nature of the disease, troublesome side effects, and symptom recurrence. Undoubtedly, sustained and controlled release systems offer many advantages in the delivery of antipsychotics, reducing the frequency of dosing and enhancing drug bioavailability [119]. Haloperidol [120], risperidone [121,122], clozapine [123], and olanzapine [124] have been, and are being, studied for long acting particulate formulations.

There are oral dosage formulations for which osmotic pumping is the major release mechanism. In this system, osmotic pressure is used as the driving force to induce drug release in a predictable and uniform manner. The osmotic pump consists of a solid core containing drug, alone or with an osmotic agent, surrounded by a semi-permeable membrane, which has a delivery pore. When this device is placed in water, the water is imbibed osmotically into the core, thereby pushing a volume of saturated drug solution through the delivery orifice in a programmed manner [125,126]. Propranolol [127], nifedipine [128], allopurinol [129], ferulate [130], diclofenac [131], and pseudoephedrine [132] have been formulated as osmotic pump controlled release formulations.

5. Types of Polymeric Pharmaceutical/Drug Delivery Particles

5.1. Microparticles for Controlled Release Delivery

Due to the development of particulate drug delivery system, current formulations in the market for delivering proteins and peptides have reduced administration from once a month to every three months. Microparticles are particles between 0.1 and 100 μm in size. Kang and Singh studied the

effect of additives on the physicochemical characteristics and *in vitro* release of a model protein, bovine serum albumin (BSA) [133]. The addition of hydrophobic tricaprין additives with low molecular weight PEG-100, results in further release of BSA from PLGA microspheres. The difference in the release profiles between control and additive containing microspheres is closely related to their surface morphology.

Blanco and Alonso compared the size effect of preparation method, w/o/w solvent extraction vs. o/o solvent evaporation, and encapsulation efficiency along with using stabilizer [134]. The size of microspheres prepared by two different methods depended on the intrinsic viscosity of the polymer solution. Microspheres using the w/o/w solvent extraction method showed a size increase, as intrinsic viscosity of the polymer solution increased, while the size of microsphere prepared by o/o solvent evaporation was increased with low viscosity polymer. Co-encapsulation of a stabilizer, poloxamer 188 or 331, induced lower loading efficiency and slower release of BSA. Without stabilizer, protein release is mainly influenced by polymer erosion rate and forming water-filled channels.

The effect of protein molecular weight (MW) on release kinetics from polymeric microspheres was studied using the phase inversion technique. The mechanism of release from microspheres appeared to be dependent on protein MW for microspheres with low loading (0.5–1.6%), whereas that is independent with high loadings (4.8–6.9%). At low loading, release of larger MW proteins was dependent on diffusion through pores for the duration of the study, while smaller MW proteins seemed to depend on diffusion through pores initially and on degradation at later times [135].

Tissue engineering in the context of controlled release drug delivery has been the subject of interesting recent research for drug delivery to bone tissue. Polymer microspheres as drug delivery carriers have been incorporated in 3D scaffolds for bone tissue controlled drug delivery [136–138]. Additionally, protein and small molecule therapeutics to promote bone growth have been incorporated in polymeric devices and in PLGA microspheres for controlled drug delivery to bone [139–143].

5.2. Nanoparticles for Controlled Release Delivery

The area of nanoparticle drug delivery is gaining much attention in recent years for a variety of administration routes, including pulmonary nanomedicine delivery [144]. To improve the bioavailability of PLGA nanoparticles, Barichello *et al.* formulated surface bound peptides using nanoprecipitation solvent displacement method [145]. Insulin was preferentially surface bound on the PLGA nanoparticles and the amount of insulin encapsulated into nanoparticles was related to composition and pH of the buffer solution; the optimal pH was close to the isoelectric point of insulin.

Insulin-loaded PLGA nanoparticles were prepared by w/o/w and s/o/w encapsulation methods with a stabilizer, Pluronic F68. Comparing the nanoparticles prepared by s/o/w method, the insulin release rate was higher for the batches prepared by w/o/w method containing stabilizers. Also the presence of stabilizers resulted in a sustained release of insulin, therefore a prolonged reduction of blood glucose level in diabetic rats [146].

Magnetically modulated nanoparticles are used for developing *in vivo* imaging and delivering drugs to targeted sites, such as tumors. Non-targeted applications of magnetic nanospheres include their use as contrast agents (MRI) and as drug carriers that can be activated by a magnet applied outside the body [147]. In another study, this magnetic force was used to improve the efficiency of orally

delivered protein therapeutics. When the external magnetic field was applied to the intestine, the transit time of magnetic particles slowed down; therefore, the residence time of the orally delivered particles in small intestine is extended and absorption of protein increases [148].

6. Manufacturing/Particle Engineering Design of Polymeric Microparticles and Nanoparticles

6.1. Double-Emulsion Evaporation Methods

As a considerable number of hydrophobic drugs are soluble in various water-immiscible organic solvent and are poorly soluble in water. By emulsion/solvent evaporation technique, both drug and biodegradable polymer are first dissolved in a solvent, mostly methylene chloride. The resulting organic oil phase is emulsified in an aqueous phase making o/w emulsion. Volatile solvents can be removed from this emulsion by evaporation [7]. However, for drugs that do not show a high solubility in methylene chloride, it can be replaced with butyl acetate, ethyl acetate, ethyl formate, or methylene ketone [7]. Alternatively, a cosolvent may be added to methylene chloride. For hydrophilic peptides or proteins, they are either dispersed in an organic solution of polymer or preferably processed in an aqueous solution of water-in-oil (w/o) emulsion resulting in a w/o or a w/o/w emulsion system [149]. However, o/w or w/o/w methods are predicted to result in low encapsulation efficiencies due to a flux of drugs from the dispersed phase to the larger volume of the continuous phase during manufacturing process [7]. In addition, proteins encapsulated by w/o or w/o/w techniques into particles are susceptible to denaturation resulting in a loss of biological activity, aggregation, oxidation and cleavage, especially at the aqueous phase-solvent interface [149]. In order to improve protein integrity, the use of stabilizers and surfactants are suggested during the primary emulsion phase.

6.2. Supercritical Fluid (SCF) Technology

Substances become supercritical fluids (SCF) when placed above their critical point, which exhibit the flow properties of a gas and the dissolving behavior of a liquid. Their solvent power is affected by density, temperature and pressure. Many excellent reviews exist on this cutting-edge particle engineering design technique that has found increasing utility in novel delivery systems for many routes of administration, particularly in non-invasive pulmonary delivery via pharmaceutical inhalation aerosols [150–153].

There are two possible processes for the drug and matrix polymer to be either dissolved or melted in the SCF and afterwards form particles following either the rapid expansion from supercritical solution (RESS) or from gas-saturated solution (PGSS) process. The RESS process, fine particles formed using the supercritical fluid as a good solvent, has two steps: (1) dissolving the solute into a supercritical fluid; and (2) formation of the solute as a microparticle due to rapid supersaturation [154]. CO₂ is an attractive solvent for a variety of chemical and industrial processes, since it is abundant, inexpensive, non-toxic, and a relatively accessible critical point, *i.e.*, T_c = 304.2 K and P_c = 7.37 MPa [154–156]. In the PGSS process, the supercritical fluid or dense gas is used as a solute. Polar or high molecular weight substances, such as proteins, are difficult to dissolve in CO₂, which has no polarity. However, the ability of CO₂ to diffuse into organic compounds enables the formation of composite particles in the PGSS process. The organic compounds will mainly constitute polymers and CO₂ lowers the

melting point and decreases the viscosity of a compound with an increase in its concentration. As a result, the compounds are melted in a compressed gas and the concentration of a gas in a molten solute increases with pressure forming a saturated solution. When this solution is rapidly depressurized through a nozzle, composite microcapsules can be formed due to the release of gas from the condensed phase [154].

6.3. Supercritical Antisolvent Method

CO₂ is the most common supercritical fluid used in pharmaceutical applications due to its relatively accessible critical point, abundance, and minimal toxicity [150,155]. In addition to RESS and PGSS, the antisolvent method utilizes CO₂ as an antisolvent for particle fabrication. Antisolvent methods have the advantage of utilizing the high miscibility of supercritical fluids with organic solvents which have high dissolving power for the compound [155]. The techniques include the supercritical antisolvent (GAS/SAS), the precipitation with compressed supercritical fluid (PCA), aerosol solvent extraction system (ASES) and the solution-enhanced dispersion by supercritical fluids (SEDS) processes. The principle of the supercritical antisolvent method (GAS/SAS) is based on a rapid decrease in the solubilization power of a solvent by addition of a second fluid as antisolvent. Adding the antisolvent expands the organic solution thereby dissolving the solute inducing supersaturation of the solution. The precipitated particles are washed with the antisolvent to remove remaining solvent [154]. Particle size can be regulated by several factors, such as temperature, pressure and composition [154]. In contrast to the one-way mass transfer of the CO₂ into the organic phase in the GAS process, in the PCA process a two-way mass transfer occurs. The organic solvent diffuses into the CO₂, and the CO₂ diffuses into the organic phase. In the ASES process, the drug and polymer are dissolved or dispersed in an organic solvent, *i.e.*, generally soluble in the supercritical CO₂, that is sprayed into a supercritical CO₂, then extracted, resulting in the formation of solid microparticles [157,158]. In the SEDS process, the particle formation is attributed to the mass transfer of the supercritical fluid into the sprayed droplet and to the rate of solvent transfer into the supercritical phase. Notably, a high mass transfer leads to a smaller particle size distribution with less agglomeration [159].

6.4. Spray Drying Particle Engineering Design

Spray drying has been widely used in the efficient design and production of food and pharmaceutical particles, especially particles designed for use in pharmaceutical inhalation aerosols [151,160]. Spray drying [151] comprises of four steps: (1) atomization of the feed solution into fine droplets in a spray; (2) spray-air contact involving intimate flow and mixing; (3) drying of sprayed droplets at elevated temperatures; and (4) separation of dried particles from the air [160]. In order to control the various particle characteristics, the operating parameters of the spray drying process such as atomization pressure, feed rate, airflow, inlet temperature, outlet temperature, and the size of nozzle orifice all must be controlled [161]. Generally, a smaller nozzle orifice, faster atomization airflow, and a low feed concentration generate a larger particle size [162,163]. To modify the particle morphology, the feed solvent type [164] or optimizing the outlet drying temperature can be done [165]. By adding Tween 20 and lactose to the feed solution, the particles with rougher surfaces can be obtained [165].

Spray-freeze drying is based on the atomization of an aqueous drug solution via a two-fluid or an ultrasonic nozzle into a spray chamber which is filled with a cryogenic liquid, *i.e.*, liquid nitrogen, or halocarbon refrigerant, e.g., chlorofluorocarbon, hydrofluorocarbon [166]. Once the liquid droplets contact the cryogenic medium, it solidifies quickly due to the high heat-transfer rate. After the spraying process is completed, the collected contents are lyophilized and frozen solvent is removed by vacuum or atmospheric freeze-drying [167]. To obtain a smaller particle size, the mass flow ratio of atomized nitrogen to liquid feed, which has the most significant influence to particle size, should be increased [168]. Spray freeze-drying can be exploited to create small microparticles and nanoparticles [169,170].

7. Marketed Controlled Release Polymeric Pharmaceutical Products and Clinical Trials

Administration of a variety of drugs encapsulated in polymeric particles has been extensively investigated leading to complete absorption of drugs in systemic circulation and control drug release over a predetermined time span in days to weeks to months, resulting in increased patient compliance and maximal therapeutic effects. Lupron[®] Depot is a microsphere formulation of leuprolide with duration of one, three or four months using PLA or PLGA in the treatment of prostate cancer and endometriosis. Nutropin[®], a commercial PLGA microsphere formulation product of human growth hormone, is used for two weeks or one month duration. As a synthetic anti-somatotropic agent for the treatment of acromegaly and endocrine tumors, Octreotide encapsulated in PLGA microspheres, commercialized as Sandostatin[®] LAR[®] is taken on a monthly basis. In addition, Trelstar[®] Depot for triptorelin, Suprecur MP[®] for busserelin, Somatuline LA[®] for lanreotide, Arestin[®] for minocycline, Risperdal Consta[®] for risperidone have been commercialized as a parenteral microsphere formulation products for extended duration [171–176]. Micellar nanoparticles incorporating paclitaxel or cisplatin are in their clinical trials [177]. There are also oral dosage formulation commercial products for which osmotic pressure is the major driving force in release mechanism, including Procardia XL[®] for nifedipine (Figure 2) and Glucotrl XL[®] for glipizide [47,48,178].

8. Conclusions

Biodegradable and biocompatible materials for pharmaceutical dosage forms have enabled the advancement of pharmaceuticals by providing better therapy and disease state management for patients through controlled release. Controlled release delivery is available for many routes of administration and offers many advantages over immediate release delivery. These advantages include reduced dosing frequency, better therapeutic control, fewer side effects, and, consequently, these dosage forms are well accepted by patients. Advancements in polymer material science, particle engineering design, manufacture, and nanotechnology have led the way to the introduction of several marketed controlled release products containing polypeptide drugs and protein drugs that retain their therapeutic activity over pharmaceutical timescales following encapsulation in biodegradable materials.

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