BIODEGRADABLE IMPLANTS WITH DIFFERENT DRUG RELEASE PROFILES

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To my parents

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1. Introduction

1.1. Parenteral controlled-release drug delivery systems

Conventional parenteral drug delivery systems, typically intravenous injection, occasionally cause a high plasma drug concentration, close to the minimum toxic concentration. Repetitive administration is sometimes required due to the short duration of action from traditional systems (Edlund and Albertsson 2002). To avoid the problems from conventional systems, parenteral controlled-release drug delivery systems are designed to achieve consistent, predictable or desired drug release profiles. They can be administered via a parenteral route either by subcutaneous injection, intramuscular injection, or injection to other specific sites such as intra-articulate injection (Burgess et al. 2002; Shi and Li 2005). Suspensions, emulsions, liposomes, microparticles and implants are identified as parenteral controlled-release drug delivery systems (Burgess et al. 2004). The systems are useful and necessary when drug candidates have poor absorption by other routes of administration and short half-lives, such as when peptides and proteins are used. Additionally, they offer benefits for patients who have difficulty with oral drug administration or are unconscious.

The advantages of parenteral controlled-release over conventional drug delivery systems are: (1) to maintain a high drug concentration in the blood circulation or prolonging the duration of action, (2) improved drug pharmacokinetics, (3) enhancement of physical stability, (4) reduction of side effects by maintaining a constant drug level via parenteral depot systems, (5) increasing specificity and reducing systemic adverse effects for targeted drug delivery, (6) an opportunity to control a precise drug release rate and (7) improvement of patient compliance by decreasing invasive administration and dosing frequencies (Senior 2000; Burgess et al. 2002; Burgess et al. 2004; Packhaeuser et al. 2004; Shi and Li 2005; Siepmann and Siepmann 2006).

Although a number of advantages of parenteral controlled-release systems are apparent, some drawbacks cannot be overlooked. Due to the many manufacturing steps required to fabricate parenteral controlled-release systems problems from scale-up, sterilization and drug stability are found (Chaubal and Roseman 2006). Dose dumping and the non-removable limitation, both are generally considered (Burgess et al. 2002). The long term stability of some formulations, for instance liposomes, is still a challenge (Shi and Li 2005).

Some parenteral controlled-release drug products have been approved and launched onto the global pharmaceutical market during the last decade (Table 1). The new drug products tend to overcome the problems of conventional systems and exhibit the benefits of parenteral controlled-release drug delivery systems. However, these drug delivery systems have been further investigated in order to achieve the better drug products required and generate novel parenteral controlled-release systems. Development of approved parenteral controlled-release systems and the introduction of novel technology by pharmaceutical scientists and formulators are in progress.

Table 1.1. Examples of parenteral controlled-release drug products (exceptional parenteral controlled-release based on biodegradable polymers) [1,2]

Product	Drug	Company	Delivery technology
Ambisome	Amphotericin	Gilead	Liposome
DaunoXome	Daunorubicin	Gilead	Liposome
Doxil	Doxorubicin	Johnson and Johnson	Liposome
Implanon	Etonogesterol	Organon	Implant
Plenaxis	Abarelix	Praecis	Carboxymethylcellulose complex
Myocet	Doxorubicin	Elan	Lipid complex

[1] (Chaubal and Roseman 2006)
[2] (Shi and Li 2005)

1.2. Parenteral biodegradable materials

1.2.1. Biodegradable polymers

Biodegradable polymers have been increasingly used in pharmaceutical applications. Ideally, biodegradable polymers would be: (1) metabolized in the body and eliminated by normal physiological pathways; (2) fabricated easily into the final forms; (3) degraded into non-toxic substances that are non-mutagenic and non-cytotoxic; and (4) cause no initiation of inflammatory processes after application, injection or insertion (Domb et al. 1999; Jain 2000; Middleton and Tipton 2000). Another criterion to be considered for a polymer to be a suitable biodegradable polymer is the end product after degradation. The end products of aerobic

degradation from biodegradable polymers should be carbon dioxide, water and/or minerals (Van der Zee 2005). According to these criteria and other necessary properties of biodegradable polymers, polyglycolide, polylactide and their co-polymers are considered as suitable biodegradable polymers.

a) Polyglycolide, polylactide and theirs co-polymer

Polyglycolide (PGA), polylactide (PLA) and theirs co-polymer are in the group of thermoplastic aliphatic poly(esters) (Jain 2000). These polymers are commercially available in different molecular weights, co-polymer ratios and chemical end groups. Interest in the use of these polymers for pharmaceutical applications and medical devices has increased extensively due to their biodegradability, biocompatibility, safety, and since they have received approval by the Food and Drug Administration (FDA) for human use (Sahoo et al. 2002; Winzenburg et al. 2004; Alexis 2005; Liu and Tomasko 2007).

PGA, PLA and copolymer, poly(lactide-co-glycolide) (PLGA) can be polymerized directly by polycondensation (either direct or melt polycondensation) of lactic acid and glycolic acid at temperatures above 120°C under water removal conditions, but this process results in low molecular polymers (Brophy and Deasy 1990; Zhou et al. 2004; Wang et al. 2006). To achieve the homo- or copolymers with higher molecular weight than a few thousand Daltons, lactide and glycolide are used as starters in the ring-opening polymerization process. Lactide (3,6-dimethyl-1,4-dioxane-2,5-dione) and glycolide (1,4-dioxane-2,5-dione) (Fig. 1.1) are the cyclic or dioxane dimers of lactic acid and glycolic acid, respectively. They are synthesized by polycondensation with or without a catalyst followed by decomposition under heat and reduced pressure (De Vries 1989; Middleton and Tipton 2000; Pham 2004). Because of an asymmetric carbon in the lactic acid molecule, two optical isomers of lactic acid (L- and D-lactic acid) occur. The resulting lactide from the two optical isomers of lactic acid occurs as three different types; L-lactide, D-lactide and DL- or meso-lactide. L-and D- lactide are optically active, while DL-lactide is an optically inactive compound (Brophy and Deasy 1990; Jacobsen et al. 1999).

The catalysts in the ring-opening polymerization are classified into two groups, metal alkoxides and Lewis-acid catalysts. Stannous octoate is in the group of Lewis-acid catalysts.

Due to its high efficiency and commercial availability it is frequently used as catalyst in this reaction. The ring-opening polymerization can be processed in bulk or in solution. The processing temperature will be higher in the bulk polymerization, because a temperature above the melting points (T_m) of the monomers is required (Jacobsen et al. 1999; Pham 2004; Zhou et al. 2004).

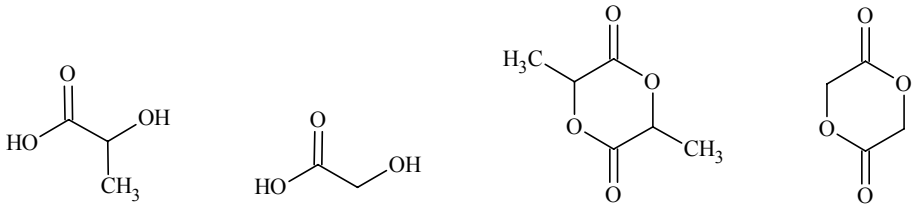


Fig. 1.1. Lactic acid, glycolic acid, lactide and glycolide

PGA is obtained by the ring-opening polymerization of glycolide (Fig. 1.2). It is highly crystalline due to the lack of methyl groups compared to PLA and has a T_m above 220°C (Lewis 1990; Jain 2000; Cameron et al. 2002). The glass transition temperature (T_g) is in the range of 35-46°C (Lewis 1990; Middleton and Tipton 2000; Cameron et al. 2002). Similar to PGA, PLA is synthesized by the same reaction using lactide as a starting material (Fig. 1.2). Because lactide exists as three dimers the type of synthetic PLA depends on the lactide used. If L-lactide is used as a starter, the product will be poly(L-lactide) (L-PLA), and using DL-lactide produces poly(DL-lactide) (DL-PLA) (Jacobsen et al. 1999; Sun et al. 2002). The thermal and mechanical properties of L-PLA and DL-PLA are dissimilar. L-PLA is mainly crystalline or semicrystalline and exhibits a T_m of approximately 150°C and a T_g of approximately 50°C. DL-PLA is an amorphous polymer. Only a T_g is observed, and it occurs at around 50°C. DL-PLA is more flexible and permeable than L-PLA. Crystallinity generally contributes brittleness to polymers, resulting in less permeability compared to an amorphous polymer (Brophy and Deasy 1990; Daniels et al. 1990; Zhou et al. 2004; Gu et al. 2008).

The common method for preparing PLGA is also the ring-opening polymerization (Fig. 2). PLGA is synthesized from DL- lactide or L-lactide and glycolide. Although, glycolide is crystalline, the copolymers of DL-lactide and glycolide, poly(D,L-lactide-co-glycolide) (DL-PLGA), with glycolide content up to 85% are fully amorphous (Zhou et al. 2004; Wang et al.

2006). The same physical solid state is found between DL-PLGA and poly(L-lactide-co-glycolide) (L-PLGA The same physical solid state is found between DL-PLGA and poly(L-lactide-co-glycolide) (L-PLGA). The resultant PLGA from L-lactide and glycolide containing glycolide in the range of 25-70% is also an amorphous polymer. This is caused by the interruption of the regularity of the polymer chain by the other monomers. Therefore, it can be concluded that PLGA will be semicrystalline when either glycolide or lactide is present in the PLGA at over 70 mol% (Middleton and Tipton 2000).

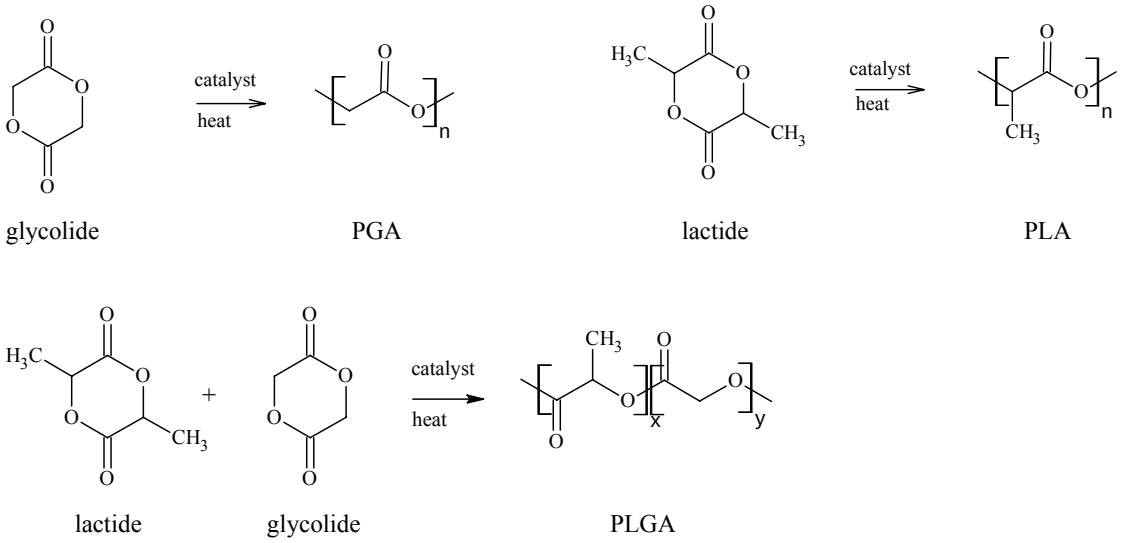


Fig. 1.2. Synthesis of PGA, PLA and PLGA

The definitions of degradation and erosion are different. Polymer degradation refers to the processes that break polymer chains down into oligomers and monomers. A decrease in molecular weight is observed when degradation occurs. Erosion of a polymer occurs after the polymer has been degraded. Erosion is the process of material loss from the polymer bulk usually resulting in a decrease of weight or mass. Phenomena such as water uptake, mass transfer and degradation are involved in the process of erosion. Therefore the polymer degradation is defined as a subset of the polymer erosion process (Göpferich 1996). In principle, erosion of polymers is classified into surface and bulk erosion. Surface, or heterogeneous erosion, takes place when the degradation of the polymer backbone is faster than the diffusion of water throughout the polymer bulk. Thus, the size of the polymer bulk is decreased as a function of time. Alternatively, if the water diffusion is faster than the polymer degradation the polymer will undergo bulk or homogeneous erosion. The polymer

degradation occurs uniformly throughout the bulk when this erosion mechanism occurs (Burkersroda et al. 2002; Winzenburg et al. 2004; Alexis 2005).

For biodegradable polyesters such as PLA, PGA and PLGA, the monomers are connected to each other by ester bonds. After water penetration into the polymer bulk the ester bonds are cleaved randomly by hydrolytic chain scission or hydrolysis. The bulk is eventually eroded through the bulk erosion mechanism. The degradation rate of PLA, PGA and PLGA can be influenced by several factors, such as, pH, molecular weight, temperature, size, additives and processing parameters (Winzenburg et al. 2004; Alexis 2005). The presence of methyl groups in the structure of PLA (Fig. 1.2) leads to more hydrophobic molecules than PGA. More hydrophobicity reduces uptake of water by the polymer backbone. PLA displays a slower degradation rate than PGA (Engelberg and Kohn 1991). The copolymer of lactide and glycolide degrades faster then the homopolymers. The degradation of PLGA is affected by the copolymer ratio. With similar molecular weights, a higher ratio of glycolide in the PLGA leads to faster polymer degradation. Since the degradation of PLGA is due to hydrolysis of ester bonds the greater hydrophilicity of glycolide results in easier copolymer hydration, thus allowing water to reach into the ester bonds in the backbone of PLGA (Ramchandani et al. 1997; Lu et al. 1999; Wu and Wang 2001; Pham 2004).

The determination of intrinsic viscosity is a way to represent the molecular weight of homo- and copolymers of lactide and glycolide. There is a linear relationship between the intrinsic viscosity and the molecular weight of these polymers. The molecular weight of the polymers affects the degradation rate in vitro and in vivo. Polymers with a higher molecular weight are degraded slower than the smaller ones (Omelczuk and McGinity 1992; Pham 2004). Molecular weight does not only influence the polymer degradation of PLA, PGA and PLGA, but the T_g and mechanical properties of the polymers are also dependent on their molecular weight. With an increasing molecular weight an increase in T_g and an improvement of the mechanical properties have been observed (Engelberg and Kohn 1991; Omelczuk and McGinity 1992; Kranz et al. 2000).

Heterogeneous bulk erosion has been observed for PLA and PLGA matrices or bulks. It occurs when the size of the polymer specimen is over a critical value. The degradation of the inner part is principally accelerated by an autocatalytic effect. With the larger size, acid

degraded products cannot easily escape or be released from the specimen. The accumulation of these acid by-products inside the specimen is the cause of the autocatalysis. Thus, the degradation throughout the bulk becomes heterogeneous. A variety of critical thicknesses or diameters have been reported. The critical size of the specimen seems to depend upon several factors, such as the type of polymer, geometrical shape and preparation methods. Therefore a unique critical thickness or diameter cannot be established (Ramchandani et al. 1997; Lu et al. 1999). Since autocatalysis by degradation products accelerates the degradation of the inner part, the porosity of polymers can have an impact on the degradation. Polymer bulks or matrices with a lower amount of porosity may result in faster polymer degradation due to the increased influence of the autocatalytic effect (Lu et al. 2000).

The addition of a hydrophilic group, such as monofunctional poly(ethylene glycol) (mPEG), onto the end of PLGA chains (Fig. 1.3) changes the water uptake of the polymer, but not the degradation. The change in the hydrophilicity of the polymer, or the water uptake, without a change in the pH can not accelerate the degradation (Zhang et al. 1997; Middleton and Tipton 2000). By contrast, the replacement of free carboxylic end groups (uncapped) with alkyl ester groups (capped) slows the polymer degradation. The degradation of uncapped polymers produces more acidic end groups, which accelerate the degradation via autocatalysis. Another reason for the faster degradation of the uncapped polymers is the faster water uptake rate (Tracy et al. 1999).

Fig. 1.3. Chemical structure of mPEG-PLGA and PLGA with alkyl ester end groups.

The addition of some additives, such as magnesium hydroxide, can modulate the degradation of PLA and PLGA. An increase in water uptake and porosity in the presence of metal salts was detected. Factors reducing the degradation were also examined. Hydroxide and carbonate salts which are sparingly soluble in water exhibited greater reduction of the polymer degradation rate compared with other salts. This phenomenon was attributed to inhibition of

the polymer autocatalysis as a result of neutralization of the acidic microclimate by the alkaline properties of the salts (Zhang et al. 1997; Zhu and Schwendeman 2000). A small number of processes and forces have been involved in alteration of polymer degradation by additives: (1) porosity induced by the additive, (2) the osmotic force, (3) neutralization by basic properties or suppression of pH reduction caused by an acidic substance from the degradation, and (4) chemical interaction between the functional group of the polymers and the additive (Zhang et al. 1997; Tang and Singh 2008).

PLA, PGA and PLGA are eventually degraded into their monomers, lactic acid and/or glycolic acid. For humans and animals these polymers can be metabolized and excreted by the normal physiological pathway (Fig. 1.4). Lactic acid is a common product of muscular contraction. Lactic acid is changed to pyruvic acid and is subsequently metabolized by the tricarboxylic acid cycle and excreted as water and carbon dioxide through respiration. Glycolic acid can be excreted directly through the urine. Additionally, glycolic acid reacts to form glycine in the body. Glycine is used to produce serine, which is afterward transformed into pyruvic acid. After going through the tricarboxylic acid cycle, pyruvic acid is excreted in the form of water and carbon dioxide (Middleton and Tipton 2000; Garvin and Feschuk 2005).

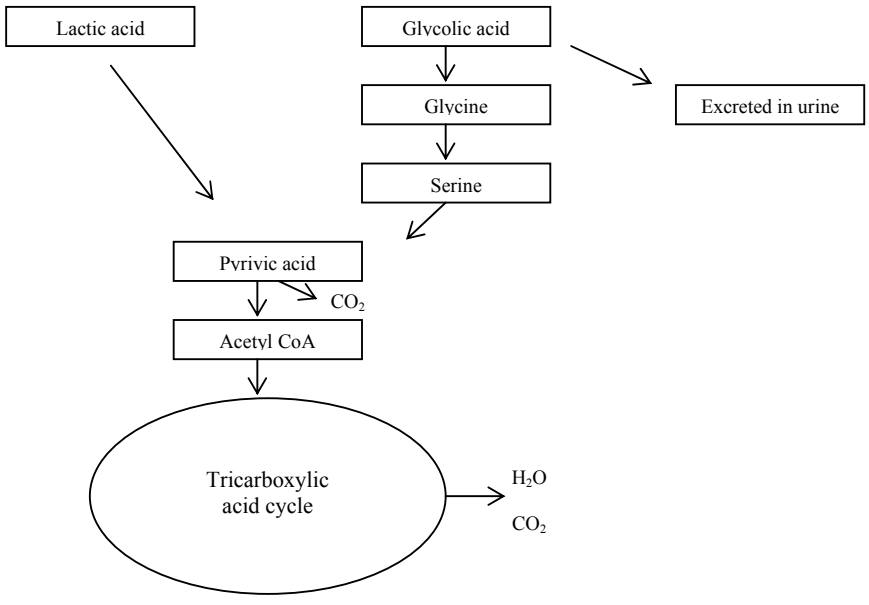


Fig. 1.4. Schematic diagram of the metabolic degradation of PLA, PGA and PLGA (adapted from Garvin and Feschuk 2005).

b) Other biodegradable polymers

A wide variety of biodegradable polymers have been used to develop parenteral controlled-release drug delivery systems. The parenteral biodegradable polymers can be fundamentally classified into two types based on their origin; natural and synthesized biodegradable polymers. Natural polymers are normally biocompatible and biodegradable (Pillai and Panchagnula 2001). Some of them have been reported as drug carriers for parenteral controlled-release systems including alginate, chitosan, collagen and gelatin. Alginate is a polyanionic polysaccharide. Gelation of alginate occurs by the addition of divalent or polyvalent cations into the polymer solution (Liu et al. 1997; Lee and Yuk 2007). Physical crosslinking using calcium ions can be used for preparing alginate beads or microparticles. The alginate solution containing the drug is added dropwise into calcium chloride solution causing alginate beads or microparticles to appear (Fundueanu et al. 1999; Yenice et al. 2002). This is a simple method to fabricate alginate microparticles for controlled-release drug delivery systems.

Chitosan is a polycationic polysaccharide, chemically poly(*N*-glucosamine), synthesized by alkaline deacetylation of natural chitin. Due to its nontoxicity, biocompatibility and biodegradability, it is also an attractive polymer for parenteral delivery of drug and biologically active compounds (Sinha and Kumria 2001). As a drug carrier, chitosan can be formulated into microparticles by spray drying or the emulsion method (He et al. 1999; Kofuji et al. 2005). A decrease in the rate of drug release from chitosan-based systems, and the gel formation of chitosan can be achieved by a crosslinking process using, for example, glutaraldehyde and divalent anions as crosslinking agents (He et al. 1999; Chenite et al. 2000). A complex of chitosan and alginate has been created via ionic interaction between the amine groups of chitosan and the carboxyl groups of alginate (Motwani et al. 2008). A more effective controlled-release was observed when using the complex of chitosan and alginate to produce the drug release system when compared to chitosan or alginate alone. A longer duration of drug release was found when the complex was used (Liu et al. 1997; Yan et al. 2001).

Collagen and gelatin are protein-based polymers. Collagen is a triple helix structure, whereas gelatin consists of single-strand molecules (Lee and Yuk 2007). Much research has reported

the development and formulation of drug delivery and tissue engineering applications based on collagen. Various small and large molecular weight drugs can be incorporated into collagen to produce dosage forms, for example gel, film and implants (Miyata et al. 1979; Fujioka et al. 1995). When collagen is used as a drug carrier, weak interactions should not be overlooked. Polyampholytic molecules of collagen generate a weak binding interaction between collagen and drugs, binding with either small or large molecular weight drugs (Wallace and Rosenblatt 2003). Gelatin is commonly used as an excipient in injection formulations instead of a dominant carrier. Gelatin by itself cannot control or prolong the drug release compared to collagen or other natural biodegradable polymers, such as chitosan and alginate (Fujioka et al. 1995). The presence of gelatin along with other polymers in the formulations influenced the drug release, with acceleration of drug release being obtained (Dordunoo et al. 1997). The crosslink or conjugation assists gelatin to become a main drug carrier. Modified gelatins have been fabricated for drug or protein delivery and tissue engineering applications. The occurrence of complexes between drugs and the gelatins promoted a longer duration of drug release or controlled-release profiles (Yamamoto et al. 1999; Rathna 2008).

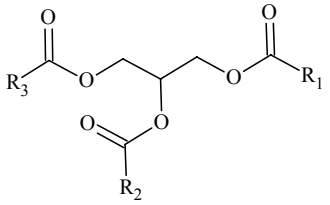
Synthesized biodegradable polymers have received increasing interest owing to the difficulty in obtaining reproducibility when using natural polymers (Angelova and Hunkeler 1999). Synthesized biodegradable polymers, excluding PLA, PGA and their co-polymers, such as poly(ε-caprolactone) (PCL) and di or triblock copolymer of PLGA or PLA with polyethylene glycol (PLGA-PEG or PLA-PEG), have been reported extensively in pharmaceutical and tissue engineering applications. PCL is a semicrystalline polymer with a low T_m (approximately 60°C) and a T_g less than 0°C (Middleton and Tipton 2000). Because of its low degradation rate, PCL is suitable for long-term drug delivery systems, which perform the release of the drug over a period of months to years (Sun et al. 2006). PCL has the potential as a carrier for tissue engineering, drug targeting and implants (Dordunoo et al. 1997; Khor et al. 2002; Coombes et al. 2004; Fialho et al. 2008). Both PCL micro- or nanoparticles incorporating drugs can be prepared (Sinha et al. 2004).

PLGA-PEG and PLA-PEG are a series of biodegradable and biocompatible block copolymers. The diblock copolymers have been synthesized by ring-opening polymerization, and continuation by coupling using hexamethylene diisocyanate results in the triblock

copolymers (Jeong et al. 1999; He et al. 2008). The block copolymers consist of hydrophobic blocks from PLGA or PLA and hydrophilic blocks from PEG (Dorati et al. 2007). The ratio of hydrophobic and hydrophilic segments, block length, hydrophobicity, polydispersity and stereo-regularity have an effect on the thermo-sensitive gel systems based on PLGA-PEG and PLA-PEG (Packhaeuser et al. 2004). The block copolymers can be formulated not only to be injectable gels, but also micelles, microspheres and in situ gel forming drug delivery systems (Yazugi et al. 1999; Zhou et al. 2001). Thermal reversible gels from the block copolymers incorporating an anti-cancer drug, hormone or protein have been established. Controlled-release over a period of a week to a month can be achieved (Jeong et al. 1999; Chen et al. 2005; Chen and Singh 2005).

1.2.2. Lipid

Parenteral lipid-based controlled-release systems have advantages because of the low toxicity of lipid carriers, which are normally the composition of physiological lipids, compared to polymeric carriers. The term lipid refers to waxes, glycerides and phospholipids. Glycerides are components of natural oils and fats (Matovic and Cees van Miltenburg 2005). As drug carriers, triglycerides have been frequently used in formula of microparticles and monolithic implants. Triglycerides are synthesized by esterification of fatty acid and glycerol under high pressure and temperature (Langone and Sant' Anna 2002). Triglycerides (Fig. 1.5) with long alkyl chains (R_1, R_2 and R_3), such as trilaurin, trimyristin, tripalmitin and tristearin, are in the solid state. The T_m of the stable crystalline triglycerides (Table 1.2) is dependent on the alkyl chains. The T_m increases with increasing length of the alkyl chains (R_1, R_2 and R_3 in Fig. 1.5) (Heurtault et al. 2003).



R_1, R_2, R_3:
$(CH_2)_{10}$ CH_3 = trilaurin
$(CH_2)_{12}$ CH_3 = trimyristin
$(CH_2)_{14}$ CH_3 = tripalmitin
$(CH2)_{16}$ CH_3 = tristearin

Fig. 1.5. Chemical structures of triglycerides

The main polymorph forms of triglycerides include the α, β′ and β-forms. The α-form is a metastable form and tends to transform into the stable β-form via the β′-form (Bunjes et al. 1996). After melting of bulk triglycerides (the β-form) followed by rapid cooling, the α-form normally occurs. Each polymorph form can be distinguished using their thermodynamic properties, X-ray diffraction patterns and T_m (Table 1.2) (Heurtault et al. 2003).

Table 1.2. T_m of polymorphic forms of triglycerides [1,2,3]

Triglycerides	T_m (°C)	
	α-form	β-form
Trilaurin	15	46
Trimyristin	33	56
Tripalmitin	45	64
Tristearin	54	73

[1] (Bunjes et al. 1996)
[2] (Robb and Stevenson 2000)
[3] (Singh et al. 1999)

Although triglyceride-based controlled-release parenteral delivery has some advantages over polymeric release systems, for example no formation of acid degradation products, the problem of polymorphic transition needs to be considered (Koennings et al. 2006). Other difficulties concern the production processes; some processes for preparing triglyceride-based drug delivery involve high temperature, pressure and/or mechanical stress, such as melt-homogenization or extrusion. The α-form probably appears after the production process, thus causing instability of the drug dosage forms. Another possible problem when using triglycerides in formulations is their stability upon storage. Changes in physical properties and drug release as a function of storage time have been observed (Bunjes et al. 1996; Reitz and Kleinebudde 2007).

1.3. Parenteral biodegradable PLGA/PLA drug delivery systems

A variety of parenteral biodegradable polymeric systems have been developed extensively over the last few decades to deliver drugs in controlled-manners. A major benefit of biodegradable dosage forms over non-degradable forms is the avoidance of surgical removal

from the body after administration. Appropriate biodegradable polymers and production techniques must be considered in order to achieve the final required dosage forms. Due to the many advantages of PLA, PGA and their copolymers, much research has been focused on biodegradable drug delivery systems based on these polymers. They are easy to be fabricated into several dosage forms (Jain 2000). A number of drug products based upon PLA and PLGA delivery systems have been launched into the global market (Table 1.3). The well-known biodegradable PLA/PLGA dosage forms are microparticles, nanoparticles, monolithic implants, in situ formed implants and in situ formed microparticles.

Table 1.3. Commercial biodegradable drug products (mainly based on PLGA polymer)

Product	Drug	Company	Delivery technology	Polymeric carrier
Decapeptyl SR	Triptorelin	Ipsen	Microparticles	PLGA
Nutropin Depot	Somatropin	Genetech	Microparticles	PLGA
Risperdal Consta	Risperidone	Janssen	Microparticles	PLGA
Sandostatin LAR	Octreotide	Novaris	Microparticles	PLGA
Trelstar Depot	Triptorelin	Watson Pharma	Microparticles	PLGA
Trelstar LA	Triptorelin	Watson Pharma	Microparticles	PLGA
Vivitrol	Naltrexone	Cephalon	Microparticles	PLGA
Profact Depot	Buserelin	Sanofi-Aventis	Solid implant	PLGA
Zoladex	Goserelin	AstraZeneca	Solid implant	PLGA
Gliadel	Carmustine	MGI Pharma	Targeting solid implant	Polifeprosan 20
Atridox	Doxycycline	Tolmar	In situ implant	PLA
Atrisorb-D FreeFlow	Doxycycline	Tolmar	In situ implant	PLA
Eligard	Leuprolide	Sanofi-Aventis	In situ implant	PLGA
Lupron Depot	Leuprolide	Abbott	In situ microparticles	PLGA

Small molecular weight drugs, anti-cancer agents, hormones, peptides, proteins and vaccines can be incorporated into PLA/PLGA microparticles and released in a controlled manner (Arshady 1991; Brannon-Peppas 1995). Microparticles are prepared mainly by three microencapsulation techniques; solvent evaporation, coacervation and spray drying (Jain 2000). Solvent evaporation with emulsification is the simplest method to obtain PLA/PLGA microparticles. The polymer solution containing the drug (in solution or dispersion) is emulsified in an external phase. The internal solvent is removed by partition into the external phase and/or by evaporation (O'Donnell and McGinity 1997). Oil-in-water (O/W) and oil-in-oil (O/O) emulsion techniques have been applied to produce microparticles using solvent

evaporation. The conventional O/W solvent evaporation is appropriate for lipophilic drugs, for instance steroids. For water-soluble drugs, peptides and proteins, low encapsulation efficiency is frequently observed (Wanteir et al. 1995). A double emulsion (W/O/W) technique has been introduced in order to circumvent the problems relating to water-soluble substances. The encapsulation efficiency was increased up to 80% or higher when using the W/O/W emulsion technique with water-soluble drugs, for instance dexamethasone salt, gonadotropin-releasing hormone and human growth hormone (Park and Kim 1999; Schwach et al. 2003; Jaraswekin et al. 2007).

The preparation of PLA/PLGA microparticles by coacervation is a complex method in which the resulting microparticles frequently agglomerate since the method lacks any stabilizers or emulsifiers (Jain 2000). A drug in the form of a solution or particles is dispersed into the polymer solution. Subsequently, the coacervation of the polymer is induced by a phase separation inducing agent. Soft coacervate droplets are hardened using another nonsolvent of the polymer, such as hexane. Large amounts of solvents are required in the coacervation process, and residual solvents are a concern for this process (Wanteir et al. 1995). Compared to solvent evaporation and coacervation, spray drying is more rapid, easier to scale up, and less dependent on factors inherent in the drugs and polymers. In the spray drying method a PLA/PLGA solution with a dissolved or dispersed drug is sprayed though the nozzle of a spray dryer to form microparticles. Dichloromethane and ethyl acetate are useful to prepare the polymer solution. The microparticles from this method are sometimes not spherical; the formation of fibers or irregular-shaped particles could be found when using this technique (Jain 2000; Schwach et al. 2003). Although drug formulations of PLA/PLGA microparticles have been successfully fabricated and launched onto the global market (Table 1.3), the inability to directly deliver drugs to targeted tissues is a problem. For this reason, nanoparticles have been developed for delivery of the drug to targeted sites.

The size of nanoparticles formed using these techniques vary between 10-1000 nm (Soppimath et al. 2001). Nanoparticles based on PLA/PLGA polymer can be produced by the same methods as microparticles (Jain 2000). Solvent evaporation with emulsification is a method to prepare PLA/PLGA nanoparticles. Homogenization, sonication or high-pressure homogenization has been used with the solvent evaporation technique for preparing nanoparticles. Either O/W or W/O/W emulsion techniques can be used to obtain the

polymeric nanoparticles (Soppimath et al. 2001; Lee et al. 2002; Rizkalla et al. 2006). In comparison with using the homogenization, sonication led to smaller particle size and narrower size distribution. Hence sonication is recommended when a particle size less than 300 nm is required (Budhian et al. 2007). Another technique involving the formation of emulsion and the salting-out process has been investigated. The aqueous phase consists of a water-soluble polymer (poly(vinyl alcohol)) and a salt in high concentration. This aqueous phase is emulsified into an organic phase containing the polymer and a water miscible solvent (acetone). The emulsion is achieved due to the presence of the salt solution. A sufficient amount of water is eventually added in order to remove acetone by its diffusion into the aqueous phase resulting in nanoparticle formation (Allémann et al. 1993; Zweers et al. 2004). An additional method to prepare PLA/PLGA nanoparticles without supplying external energy is nanoprecipitation. Both the polymer and a drug are dissolved in the first solvent (termed the solvent) after which the solution containing the drug and polymer is added into a second solvent (termed the anti-solvent) which is miscible in the first solvent. The nanoparticle formation occurs as a result of a desolvation of the polymer (Bilati et al. 2005; Budhian et al. 2007). A dialysis method is applied for PLA/PLGA nanoparticle preparation. The polymer and a drug are dissolved using an organic solvent. The polymer-drug solution is afterwards loaded onto a dialysis membrane and dialyzed against an external aqueous phase (Xie and Wang 2005). Small particles (less than 500 nm) are typically present if the nanoprecipitation and dialysis method are chosen as the method for nanoparticle preparation (Bilati et al. 2005; Budhian et al. 2007; Zhang et al. 2008).

An alternative method to produce micro- and nanoparticles is supercritical fluid technology. To produce solvent-free micro- and nanoparticles in an environmentally responsible manner, the use of carbon dioxide as a solvent or nonsolvent for preparing PLA/PLGA micro- and nanoparticles has been reported. The solutes of interest (usually PLA/PLGA and a drug) are solubilized in supercritical carbon dioxide as a solvent and then sprayed through a nozzle. The solutes eventually precipitate to yield particles with sizes ranging from a few microns up to several hundred microns. This process is known as rapid expansion of supercritical solution (RESS). The limitation of the solute solubility in supercritical carbon dioxide is a disadvantage of RESS. To overcome this limitation a process called supercritical anti-solvent (SAS) has been developed. Usually the solutes (PLA/PLGA and a drug) are practically insoluble in supercritical carbon dioxide, while a solvent is miscible with the supercritical

fluid. In this process the solutes are recrystallized to form small particles upon contact with the supercritical fluid. Solvents, such as acetone, dichloromethane and dimethyl sulfoxide (DMSO) have been used as the solvent for the PLA/PLGA and drug mixture in the SAS process (Subramaniam et al. 1997; Soppimath et al. 2001).

Residual organic solvents remaining in the final products are an important drawback to be considered when preparing microparticles and nanoparticles (Jain 2000). In comparison with micro- and nanoparticles, some processes to prepare solid implants can avoid the use of organic solvents. Moreover, a solid implant is a dosage form which has some advantages over microparticles and nanoparticles. It can administer directly to the targeting side of action including intraocular and intracerebrospinal (Yasukawa et al. 2001; Benoit et al. 2003). (The advantages and disadvantages of implants and immune reaction to the biodegradable PLGA/PLA implants will be discussed in depth in 1.4.)

A novel implant system known as in situ forming implants has been discovered. PLA/PLGA was dissolved in a biocompatible organic solvent after which a drug was added into the polymer solution to obtain the final drug solution or dispersion. As the final preparation is in liquid form, it is injected intramuscularly or subcutaneously into the body using a syringe and needle. The injectable solution solidifies upon exposure to the physical body as a result of polymer precipitation or coagulation, forming a drug depot at the site of injection (Jain 2000; Packhaeuser et al. 2004; Kranz and Bodmeier 2007). Surgical incision can be avoided when using this novel dosage form (Tang and Singh 2008). Moreover, less complicated preparation and less stressful preparation conditions are also advantages of in situ forming implants (Packhaeuser et al. 2004). PLGA or PLA polymer can be formulated as in situ devices based on polymer precipitation. Promising solvents for the preparation of PLGA/PLA in situ implants are N-methyl-2-pyrrolidone (NMP), DMSO, 2-pyrrolidone, triacetin and polyethylene glycol (PEG). The effect of solvent used, polymer concentration and molecular weight of polymers on the drug release have been investigated. All of these parameters influence the rate of the polymer precipitation and the initial burst release, which is a major drawback of the system. The initial burst release was inversely proportional to the polymer concentration (Lambert and Peck 1995). The use of a solvent which exhibits a faster phase inversion caused the high burst release. Additional disadvantages of in situ implants are

myotoxicity from the solvents and the difficulty of administration due to the high viscosity of the polymer solution (Kranz et al. 2001; Hatefi and Amsden 2002; Packhaeuser et al. 2004).

In situ forming microparticles have been formulated in order to overcome the drawbacks of in situ forming implants. The difference between in situ forming microparticles and implants are the supplementary preparation process prior to the injection. A drug and the polymer are dissolved in a biocompatible solvent to be an internal phase. The internal phase is afterward emulsified into an external phase. The external phase can be oil for injection (O/O in situ microparticles) or aqueous (O/W in situ microparticles) containing a stabilizer. This dispersion or emulsion is injected into the body. The internal phase solidifies upon contact with the body fluid, and thus forms microparticles at the site of injection. In comparison to in situ implants, the presence of the external phase was reported to reduce myotoxicity from the solvent used and initial burst release. The lower viscosity of the in situ microparticle formulation is additionally an advantage over in situ implants. The viscosity of the in situ microparticle formulation was dominated by the viscosity of the external phase, which is less than the viscosity of the polymer solution. This results in easier injection and less pain during injection (Kranz et al. 2001; Luan and Bodmeier 2006; Rungseevijitprapa et al. 2008).

1.4. Implants

Implants are dosage forms, which are inserted into the body subcutaneously or into a body cavity with the aid of surgery or the use of particular needle (Shi and Li 2005; Iyer et al. 2006). In case of non-biodegradable implants, a second surgical procedure is needed to remove the devices. Although the invasive procedures are a major disadvantage of the administration, implants can be able to remove easily if early termination is required owing to adverse effects. To overcome drawbacks of conventional parenteral dosage forms, implant delivery systems have been designed to reduce the frequency of dosing, to prolong duration of action, to increase the patient compliance, and mainly to optimize pharmaceutically-related therapy (Nitsch and Banakar 1994; Shi and Li 2005; Iyer et al. 2006).

Implants can be used as delivery systems for systemic or local therapeutic effects. For systemic therapeutic effects, implants are administered subcutaneously (SC) (Shi and Li 2005). An incorporated drug is delivered from the implant and absorbed into the blood

circulation. Implants for local effects are placed into specific body sites. The term “local injection” is the drug administration to local compartments where the drug action occurs without being absorbed into the systemic circulation. Targeting implants aim to release a drug and have a therapeutic effect at the sites of implantation (Senior 2000).

There are a few commercial non-biodegradable implants, which have been available in the drug market. Some of them are contraceptive implants and aim to represent a systemic therapeutic effect. Norplant® is a well-known contraceptive implant approved by U.S. Food and Drug Administration (FDA) in 1990. The system composes of six silicone rubber tubes containing 36 mg of levonorgesterol. The implants release the drug for up to 5 years. Another contraceptive implant is Implanon®. It is a single-rod implant coated by ethyl vinyl acetate. Implanon® contains 67 mg of etonogestrel and releases the drug over 3 years. For the treatment of cancers, a hydrogel reservoir delivery system made from a crosslinked copolymer of hydroxypropyl methacrylate and 2-hydroxy methacrylate. Vantas® implant is a hydrogel reservoir implant and used to the treatment of metastatic prostate cancer. The drug core of the system contains histrelin acetate. The implant has to be soaked in sodium chloride solution before insertion. The polymer wall allows hydrating and the drug is released over a 12-month period. The hydrogel reservoir implant leads to less uncomfortable feeling in comparison with other metal implants (Shi and Li 2005).

Intracerebrospinal, intraventricular, intra-articular and intraocular are recognized as local injection or implatation (Senior 2000). Insertion into the specific sites of action leads mainly to local effects of drugs. Implant dosage forms have been reported to be used as drug targeting devices for all local sites of action. Normally at the specific targeting sites, such as the sclera and the brain, low level of drug is achieved when a systemic dosage form is applied. Implants can overcome this drawback of systemic administration. Implants containing an antibiotic or an antiviral drug were designed and inserted into either bone or sclera, which are the areas of low blood circulation, for the treatment of local infection. The drug concentration at the site of action was prolonged and higher than minimum inhibitory concentration against pathogens (Kunou et al. 2000; Castro et al. 2005; Kälicke et al. 2006). Not only antimicrobial drugs but also some steroids or other small molecular weight drugs can be incorporated into implants. They aim to release the drugs at the targeting sites for a local effect (Felt-Baeyens et al. 2006; Klose et al. 2009).

Another disadvantage of implant drug delivery system is fibrous encapsulation created by the foreign body reaction. An insertion of an implant for long term drug delivery leads to a formation of fibrous capsules, which is the end product of the body reaction for a large foreign body. The fibrous encapsulation could cause an undesirable effect on drug release from an implant (Ratner 2002). The fibrous or collagen capsule is a barrier of drug diffusion and separated the implant from blood capillaries (Hetrick et al. 2007). The thickness of the capsule can not be predicted. It results into unpredictable drug release (Ratner 2002). Several methods have been explored to overcome this problem. Reducing diameter of biodegradable fibers was a method to decrease thickness of capsules generated by the foreign body reaction. Less thickness of fibrous capsules was observed by the fibers with diameter less than 5 μm (Sanders et al. 2002). Nitric oxide and polymer blend were successful to reduce the foreign body reaction. Nitric oxide release from the coating silicone elastomer implant could decrease the formation of the foreign body capsule. However, the preparation to incorporate into the implants nitric oxide into the implant was complicated. Blending PLGA with 2-methacryloyzyethyl phosphorylcholine and 2-ethylhexyl methacrylate copolymer also showed also a reduction of inflammation reaction. This material provided a good trend to further achieve a material with less induced foreign body reaction (Iwasaki et al. 2002; Hetrick et al. 2007).

Since the last few years, there is a commercial targeting implant on the drug market, which is so-called Gliadel® Wafer. It contains carmustine and is approved for the treatment of glioblastoma multiforme. The solution of carmustine and copolymer of 1,3-*bis*(*p*-carboxypenoxy) propane and sebacic acid in the ratio of 2:8 in dichloromethane is used to prepare microspheres by the spray drying process. The microspheres are then compressed into a wafer (14.5 mm in diameter and 1 mm in thickness). Gliadel® Wafer is inserted into the surgical cavity at the time of operation. It releases the drug over 5 days and the copolymer degrades at the site of action with 8 weeks (Shi and Li 2005).

1.4.1. PLGA- and PLA-based biodegradable implants

To overcome the drawback of non-biodegradable implants, biodegradable implants based on PLGA or PLA polymer have been developed. Due to the wide uses as polymer for surgical sutures, the approval by US FDA for parenteral administration and the ease to be shaped into

an implant by several techniques, using PLGA and PLA as a carrier for biodegradable implants have more benefit than other polymers (Rothen-Weinhold et al. 1999; Lü et al. 2009). Moreover, they can be degraded into the acidic by-products and be eliminated by the normal pathway from the body, thus avoiding a removal process after the end of drug duration (Jain 2000; Dorta et al. 2002; Gad et al. 2008). However, PLGA and PLA degrade into the acidic by-products, which can induce the undesired foreign body reactions. In comparison to metal implants, biodegradable implants are more expensive due to the cost of the polymer carriers (Akmaz et al. 2004).

There are two available commercial products on the drug market. They have been fabricated to use for the treatment of prostate cancer. A biodegradable implant containing goserelin acetate, which is decapeptide analogue of lutinizing hormone releasing hormone (LHRH), is so-called Zoladex®. It uses PLGA or PLA as a carrier for the drug delivery system. The drug is dispersed in the polymer matrix using hot-melt extrusion method and the implant is distributed in the form of a prefilled syringe. The drug is continuously released over a period of 1 or 3 months (Hutchinson and Furr 1987; Shi and Li 2005; AstraZeneca Canada 2010). Profact® Depot or Suprefact® Depot contains buserelin acetate. The trade name of this product depends on available locations. It is called Profact® Depot in Germany. PLGA in a 75:25 molar ratio (the ratio of lactide to glycolide) is used as a drug carrier. Profact® Depot implant has been designed for 2- and 3-month drug release. The duration of action is different due to the amount of drug and PLGA in the implants. 9.9 mg of buserelin acetate and 39.4 mg of PLGA are fabricated for each 3-month depot, whereas 6.6 mg of buserelin acetate and 26.4 mg of PLGA are produced for each 2-month implant (Sanofi-Aventis Canada 2010).

Various types and properties of drugs can be incorporated into PLGA or PLA implants (Sanders et al. 1986; Zhou et al. 1998; Lin et al. 2001; Dorta et al. 2002; Park et al. 2011). For drugs with small molecular weight, antibiotics, antiviral drugs, anticancer drugs, analgesics and steroids have reported to be incorporated into PLGA and PLA polymer for preparation of implants (Zhou et al. 1998; Yasukawa et al. 2001; Dorta et al. 2002; Qian et al. 2004). They can also deliver peptides and proteins, such as LHRH analogue (Zhu and Schwendeman 2000). Although the acidic by-products can cause instability of proteins (Zhu and Schwendeman 2000), some therapeutic proteins are found to deliver by PLGA or PLA implants, such as recombinant human growth hormone and insulin (García et al. 2002;

Santoveña et al. 2006; Naha et al. 2009). The physicochemical properties of drugs play a role in drug release from PLGA- or PLA-based implants. The implants containing a highly water-soluble drug showed a large initial burst release followed by a rapid release. Drug loading has also an impact on the release rates. With a high drug loading, a fast release of a drug form the biodegradable implants can be observed (Dorta et al. 2002; Wischke and Schwendeman 2008). Some drugs incorporated into PLGA or PLA implants aim to release at the sites of action, which is an advantage of drug delivery implants particularly PLGA- or PLA-based implants. Steroids and antiviral drugs can be delivered by the biodegradable implants into ocular cavities or tissues (Kunou et al. 1995; Kunou et al. 2000; Okabe et al. 2003). Moreover, antibiotics and anticancer drugs have been loaded into the biodegradable implants for local therapeutic effects. Biodegradable implants containing an antibiotic, such as gentamicin or ciprofloxacin, have already existed. They aim to treat complicated bone infections, for which a systemic administration is not fully effective (Castro et al. 2005; Aviv et al. 2007). Anticancer drugs, for example 2-methoxyestradiol, paclitaxel and doxorubicin, can be delivered by the biodegradable implants for the treatment of cancer (Weinberg et al. 2007; Desai et al. 2008; Lee et al. 2009). Some implants are designed to administer intratumorally or near a tumor after an operation. By this way, an anticancer drug has its effect at the site of action. They are used to prevent or reduce tumor recurrence (Weinberg et al. 2007).

1.4.2. Processes for preparing PLGA/PLA implants

Various preparing techniques have been used to prepare PLGA- or PLA-based implant drug delivery systems. Cylindrical, disk and square geometrical implants are designed. Heating, solvents and/or compression pressure are involved in processes. The possible and available methods for fabricating implant drug delivery are as follows:

a) Compression

Compression is a possible method for a preparation of PLGA- or PLA-based implants. The preparation of implants by compression is the lack of heat and solvent (Jivraj et al. 2000). It is a less stressful method in comparison with the other processes, for example injection molding and hot-melt extrusion. Therefore, it is a suitable method for drugs, proteins or peptides, which are sensitive to moisture, solvent and heat (Fujioka et al. 1995). Three

mechanisms are involved in the process of compression. Fragmentation occurs and powders are fractured into smaller size. Subsequently, changes in shape of powders known as deformation are usually observed. Powders are then moved closer to reduce porosity, and thus densification (Armstrong 1989; Johansson and Alderborn 2001; Wu et al. 2008).

The implants prepared by this method sometimes show a fast release with a short duration (Negrín et al. 2004; Onishi et al. 2005). Additional methods to suppress or prolong a drug release prepared by direct compression are necessary (Huang and Brazel 2001; Qian et al. 2001). Compressed heat and coating have been introduced. Heating and compression lead to high density of PLGA implants and the drug release is slower. Coating after compression is also a useful method to slow the drug release due to an additional layer. A drug has to diffuse through the coating layer, and thus retarding the release. The combination of compression and heating or coating is successful to delay a drug release from the biodegradable implants, but these methods need heat or a solvent to form a coating layer. That makes compression to be less advantage over other methods (Wang et al. 1996; Qian et al. 2001; Negrín et al. 2004).

b) Solvent associated methods

Biodegradable implants, particularly PLGA- or PLA- based implants can be prepared by methods associated solvents. Solvent casting and solvent extrusion are included. For solvent casting, PLGA or PLA is first dissolved in an appropriate solvent that can dissolve the polymers, for example dichloromethane and trichloromethane. The polymer solution is then casting into a mold, which is usually a Teflon mold. The solvent is then evaporated at room temperature or a low temperature in order to control the evaporation rate. Finally, the biodegradable film is vacuum-dried to remove the residual solvent (Dorta et al. 2002; Santoveña et al. 2006; Umeki et al. 2011). Biodegradable implants prepared by solvent casting always result into films or laminar implants. The implants can release a drug over a period of weeks to months. It also depends on the types of biodegradable polymers. A duration of action over several months is always demonstrated when using PLA as a carrier (García et al. 2002; Tarantili and Koumoulos 2008; Umeki et al. 2011).

Another solvent associated method is solvent extrusion. Firstly, a suitable volatile solvent is used to dissolve the biodegradable polymers. A high concentration of the polymer solution is

required. The polymer solution is then extruded by force through a small orifice. The solvent is allowed to evaporate and an extrudate is finally formed. For laboratory scale, a syringe and a silicone tube can be used in the process of solvent extrusion. A polymer solution is extruded through a syringe connected to a silicone tube at the open end. The silicone tube helps a wet extrudate to form a required shape during solvent evaporation (Zhu and Schwendeman 2000; Desai et al. 2008). An additional process is necessary when drug powders have to be dispersed in a high concentration of polymer solution. Micronization can solve this problem. The drug powders will be dispersed and suspended homogenously in the polymer solution before extrusion (Zhou et al. 1998; Desai et al. 2008).

A drawback of the solvent associated methods is a presence of an organic solvent in the formula. Therefore, stability of incorporating drugs is commonly concerned, particularly therapeutic proteins. It is necessary to test the stability of a drug in the solvent in order to determine a contact time. This will be ensured drug stability when a drug has to contact with an organic solvent (García et al. 2002; Santoveña et al. 2006).

c) Injection-molding

Injection-molding was introduced to use as a pharmaceutical technique since 1964. It was previously a technique for plastic industries. A thermoplastic polymer is molten and injected into a specific mold. The molten polymer is solidified in the mold. A matrix tablet or implant is then achieved (Quinten et al. 2009). The process is reproducibility and automatization. A tablet of an implant with desirable size and shape is easily obtained by injection-molding (Wu et al. 2006). Biodegradable polymers, particularly PLGA and PLA, can also be shaped in the form of an implant by injection-molding (von Oepen and Michaeli 1992). Due to the exposure to heat of the process, a decrease in molecular weight of the biodegradable polymer is a problem of injection-molding when so high temperature is applied. A temperature range of 80 – 140 °C by this method is suitable for the biodegradable polymer (von Oepen and Michaeli 1992; Rothen-Weinhold et al. 1999). A peptide, such as vapreotide, can be incorporated into PLA or PLGA by using injection-molding. The system intended to deliver the peptide for a long duration of action. A few percentage of peptide degradation was reported. Therefore this process can be useful for the development of PLGA- or PLA-based drug delivery systems (Rothen-Weinhold et al. 1999).

d) Ram extrusion

Ram extrusion is a process relating to force and high pressure (Baert et al. 1992). It is a reciprocating (discontinuous) extruder (Rauwendaal 2001). Heat is usually applied on this process where a plunger presses on a soften polymer (Gurtler et al. 1995). PLGA- or PLA-based implants can be prepared by ram extrusion. Processing temperatures for extrusion of PLGA and PLA polymers should be above their T_g. The polymer is then softened enough to be forced through a die (Rothen-Weinhold et al. 1997; Witt et al. 2000). Since the process involving heat and pressure, a stability of an incorporating drug has to take in consideration. Dugs, which are unstable to heat and high pressure, can not be prepared by this method without a process optimization. For therapeutic peptides and proteins, stability under a stress condition as the high temperature and pressure in a ram extruder is an important issue. At the temperature of 80°C, small amount of degradation or impurity have been found. An increase in the amount of impurity resulted from the ram extrusion at high temperature (above 120°C) for long extrusion time (Rothen-Weinhold et al. 1999; Rothen-Weinhold et al. 1999; Rothen-Weinhold et al. 2000). Similarly, high temperatures and pressure affect on molecular weight of PLGA and PLA. A decrease in number of molecular weight was reported when the biodegradable implants were fabricated by ram extrusion (Ferguson et al. 1996; Rothen-Weinhold et al. 1999).

e) Hot-melt extrusion

Melt processing is widely used as a method to prepare biodegradable monolithic implants, particularly for commercial products (Breitenbach 2002; Sarazin et al. 2004). It is a method, which is used most in plastic industries (Rosato and Rosato 1995). Melt extrusion or hot-melt extrusion is briefly the process of melting, mixing, and forcing a mixer containing thermoplastic material through a small orifice called a die. Usually the process is performed under an elevated temperature (Breitenbach 2002; Crowley et al. 2007). By this preparing method, PLGA- or PLA- based implants are basically a matrix system. The drug is dispersed uniformly through put the implants. Depending upon type of melt-extruder, premixing is sometimes required to blend the polymer with the drug to obtain a homogeneous extrudate (Sanders et al. 1986). The polymer carriers, which are PLGA or PLA for biodegradable implants, are molten and act as a thermal binder (Crowley et al. 2007). To fabricate PLGA or

PLA implants, an operating temperature above their T_g has to be applied. By contrast, too high temperature is not allowed, because incorporating drugs can be thermally degraded. The optimal extrusion temperature is in the range of 50-100°C (Bhardwaj and Blanchard 1998; Schwach et al. 2003; Kovalchuk et al. 2005; Amann et al. 2010; Wang et al. 2010). The difference in the temperature depends on drug loading, type and molecular weight of the biodegradable polymer, and type of hot-melt extruders. (More information about hot-melt extrusion is revealed in the next topic.)

Hot-melt extrusion for preparation of the biodegradable implants can considerate as an effective method. It is a continuous process and suitable for industrial productions (Wang et al. 2010). A solvent or water is not necessary for hot-melt extrusion (Crowley et al. 2007; Wang et al. 2010). A drug, peptide or protein, which is sensitive to organic solvents or water, can be incorporated into the biodegradable implants, for example degarelix (Schwach et al. 2003). In comparison to the solvent associated methods (double-emulsion solvent evaporation and spray drying) and ram extusion, degarelix was more stable the drug delivery system was prepared by hot-melt extrusion. The finding was explained by the shielding effect. Hot-melt extrusion improved the dispersion of the peptide in PLGA matrix resulting into more shielding effect (Schwach et al. 2003). The peptides, nafarelin and melanotan-I, were tested regarding to the biological activities. The lost of biological activities after preparing by hot-melt extrusion was negligible (Sanders et al. 1986; Bhardwaj and Blanchard 1997). Moreover, hot-melt extrusion is also an appropriate method to produce PLGA implants containing a protein. Although the process involves in heat and high pressure, an incorporating model protein as lysozyme was recovered with biological activity (Ghalanbor et al. 2010).

For small molecular weight drugs, the biodegradable implants can be used for a drug, which aims to release the drug over duration of weeks to months or to release the drug at the site of action (Viitanen et al. 2006; Amann et al. 2010). Antipsychotic and anti-imflammatory drugs, for example haloperidol and diclofenac sodium, have been loaded into the biodegradable implants by hot-melt extrusion (Viitanen et al. 2006). The drug loading could be up to 40% by weight and prolonged-releases are shown. The drug release profile showed a similar bi- or triphasic release as in implants prepared by the other methods. However, the first phase of the

profiles is different. Due to the production of a dense matrix implants, no release or less burst release could be obtained (Amann et al. 2010; Wang et al. 2010).

1.5. Hot-melt extrusion

Approximately 40 % by weight of all plastics has been recently produced though extruders (Rosato and Rosato 1995). Extrusion, particularly hot-melt extrusion, was first introduced to the plastic industries in the nineteenth century. It has been afterward applied in the field of pharmaceutical industry (Crowley et al. 2007). Hot-melt extrusion is simply defined as a process of converting a raw material into a finished product (termed an extrudate) by forcing them through a die and applying heat at the same time (Breitenbach 2002; Mollan 2003). The material, which is a mixture of a thermoplastic polymer or lipid and a drug, is firstly molten to be a viscous solution inside the barrel of the hot-melt extruder. The soften mixture is then mixed and conveyed by a screw or two screws depending on the models of hot-melt extruder. It is forced eventually through a die (McGinity and Zhang 2003).

The unit operations of pharmaceutical-class hot-melt extruders and plastic extruders are virtually similar. The differences are the contact parts of extruders. The contact parts of pharmaceutical-class extruders have to be composed of inert and nonabsorptive compounds (Crowley et al. 2007). There are many advantages of hot-melt extrusion in the view of pharmaceutical industry and drug product development. It is a continuous producing process with high throughput rate. The process does not need a solvent or water (an anhydrous process). Processing steps are decreased in comparison with other industrial scale productions. It can be considered as a single unit operation resulting into shorter time to final drug products. Intense mixing occurs, which leads to de-aggregation of suspended particles and thus more uniform dispersion. It can be an effective method to use for improving bioavailability of poorly water-soluble drugs by an increase in drug solubility (Breitenbach 2002; Mollan 2003; Crowley et al. 2007; Repka et al. 2007).

In order to achieve a drug product by hot-melt extrusion, a high temperature above T_g or T_m of a drug carrier has to be applied. The extrusion temperature has to be usually set 15-60°C above T_g or T_m of the carrier. Moreover, drugs, carriers and excipient have to contact with a high mechanical stress produced by rotating screws. Under these stress conditions, chain

scission, depolymerization and/or thermal degradation are easily happened. Therefore, drugs, carriers and excipient must be thermally stable at the extrusion temperature and resistant to a high pressure along the duration of hot-melt extrusion process. (Crowley et al. 2007).

1.5.1. Hot-melt extruders

A hot-melt extruder consists of mainly three sections: feeding zone, transition zone and metering zone (Fig. 1.5). A starting material is feed through a hopper into the feeding zone. The material is prepared to be conveyed along the barrel. A solid plug from the feeding zone is entered the transition zone. At this section, the material is molten, mixed, and compressed (Chokshi and Hossein 2004). The mixture in the hot-melt extruder is moved along the barrel due to friction between the mixture, barrel and rotating screw. The friction on the surface of barrel is the driving force for an extruded material. During the movement heat is applied to soften or melt the extruded material. Heating for a hot-melt extruder is generated by two sources: shearing of the rotating screw and electrical heating system (Crowley et al. 2007). The temperatures created by two sources are detected by thermocouples and displayed as an extrusion temperature (McGinity and Zhang 2003). The material eventually reached the metering zone in the form of a molten uniformly mixture. The metering zone functions as a flow reducer and a controller to control a rate of an outcome, which is so-called an extrudate (Chokshi and Hossein 2004).

Hot-melt extruders are classified into single screw and twin screw extruders. Single screw extruders were firstly introduced in the late 1800s. The patent of the first single screw extruder claims that the apparatus is used for cooling, conveying, and mixing soap. It combines separate unit operations to a single unit operation (Mollan 2003). Single screw extruders are principally simple machines. One screw rotates in the barrel and is used for solid transportation, melting, mixing and pumping. A barrel covers the screw and contains three or more heating zones to elevate temperatures at the screw and barrel until meeting a desirable temperature. Pressure inside the barrel is generated by melting and mixing viscous materials, and pumping them through a die (Luker 2003; Crowley et al. 2007). Twin screw hot-melt extruders have been also developed by the concept of including many available devices into a single unit. Two screws inside a barrel arrange side by side. The screws can rotate in the same direction, called co-rotating screws, and in the opposite direction, called

counter-rotating screws. Co-rotaing screws are normally an intermeshing design. They are self-wiping, and then operate by a first in/first out principle. Counter-rotating screws are required when very high shear forces are needed. In general, air entrapment and high-pressure generation are problems of counter-rotating screws. They have to operate at a low screw speed to avoid the disadvantage of building up too high pressure inside the barrel (Breitenbach 2002; Mollan 2003; Crowley et al. 2007).

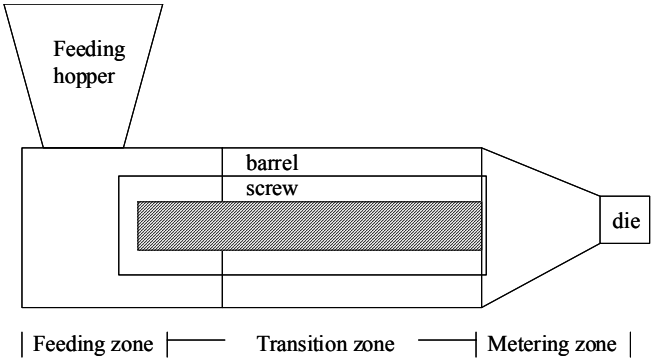


Fig. 1.5. Schematic diagram of a hot-melt extruder in a horizontal view

The key differences between single and twin screw extruders are the conveying mechanisms and the mixing ability. Hot-melt extrusion by single screw extruder depends on the frictional and viscous properties of the processing materials. Because the fictional forces in the solid conveying zone and the forces from viscous materials in the melting zone cause the material transportation in the barrel. For twin screw extruders, conveying and mixing happen due an agitation of two screws. Material is exchanged from one to another screw to achieve a homogeneous mixture. At the same time, mixing occurs through the high-shear area between two screws (Mollan 2003). Moreover, the advantages of twin screw over single screw hot-melt extruder except mixing ability are as follows: shorter residence time, self wiping screw, minimum inventory and versatility (Breitenbach 2002).

A feed hopper is connected to the feeding section in the barrel of a hot-melt extruder. When a mixture is fed to this part, the angle of repose of the mixture is taken into consideration. Ideally, the angle of feed hopper should exceed the angle of repose of the mixture. If this requirement is not matched, there is a tendency to form a solid bridge at the neck of the hopper. To solve this problem, a force-feeding device can be used to feed directly on the

rotating screw. Feeding is normally separated into flood and starve feeding. Single screw extruders need principally flood feeding (Crowley et al. 2007). Otherwise an output will be depended on both screw speeds and feed rates. If an amount of feeding materials can replace immediately an empty space of the single screw, the output of a single screw extruder is only dependent on the screw speed. Twin screw extruders are designed to be starve fed. An increase in feed rate results in a decrease in the effective shear rate (Dreibatt 2003).

1.5.2. Application in pharmaceutical dosage forms

Recently, hot-melt extrusion has become more interesting process for fabricating pharmaceutical dosage forms due to the advantages over conventional preparing methods. More than a hundred scientific articles in the field of pharmaceutical hot-melt extrusion have been published in the last decade and the numbers of patents have increased continuously (Crowley et al. 2007). Various dosage forms, such as pellets, tablets, implants and transdermal patches, have reported to be fabricated by this technique (Sanders et al. 1986; Young et al. 2002; Six et al. 2003; Fukuda et al. 2006; Mididoddi and Repka 2007). Most of them aim to achieve a prolonged or controlled drug release, to increase drug solubility and to reach stable pharmaceutical dosage forms by hot-melt extrusion.

Hot-melt extrusion is an effective method to prepare pellets, tablets and capsules for oral drug delivery systems. Pellets can be obtained by a traditional spheronizer after hot-melt extrusion. Hot-melt extrudates are cut into a symmetrical rod and spheronized at elevated temperatures (Young et al. 2002). Tablets are easily shaped by cutting a hot-melt extrudate into a mini-tablet with desirable thickness. A good selection of drugs, polymers and additives helps design tablets or capsules to release at targeting site of action in the gastrointestinal tract (Bruce et al. 2005; Mehuys et al. 2005). The addition of sodium bicarbonate into hot-melt extrudated tablets resulted to floating tablets in the acidic media with a long floating time (Fukuda et al. 2006). A blend of a hydrophobic and a hydrophilic polymer represented a time independent drug release and a sustained drug release when preparing tablets by hot-melt extrusion (De Brabander et al. 2003). Moreover, high drug loading matrix tablets with sustained or controlled drug release have been fabricated successfully. The drug loading up to 60-65% by weight has been reported (De Brabander et al. 2003; Özgüney et al. 2009).

Due to problems from a preparation of films for transdermal or transmucosal drug delivery by solvent casting, hot-melt extrusion is a better choice for a production of films. Using solvent casting to prepare films, physical aging and mechanical instability occur (Repka et al. 2007). The physical and mechanical properties of films from polyethylene oxide or a blend of polyethylene oxide and hydroxylpropyl cellulose prepared by hot-melt extrusion were not changed after several months at 25°C/60% RH. The extruded films seem to be stable along the investigated time (Crowley et al. 2004; Prodduturi et al. 2005; Prodduturi et al. 2007). An increase in drug permeability and an improvement in bioadhesion were reported for the films prepared by hot-melt extrusion (Repka et al. 2004). Therefore, hot-melt extrusion is helpful for design and formulation of transdermal or transmucosal drug delivery systems.

1.5.3. Excipient for hot-melt extrusion

a) Carriers

Thermoplastic polymers are suitable for hot-melt extrusion (Breitenbach 2002). Thermoplastic properties are basically required to produce the polymers into a dosage form (Chokshi and Hossein 2004). The polymers have to be softened or molten when heated above their T_g or melting points and the properties must be reversible after cooling. With this preparing method, polymers can be considered as thermal binders and/ or drug retardants for pharmaceutical drug delivery systems (Crowley et al. 2007). Drug-polymer compatibility, polymer stability, drug release kinetics and route of administration are taken into account when choosing a polymer as a carrier for hot-melt extrusion (Chokshi and Hossein 2004; Crowley et al. 2007). A selected polymer has to be compatible with the drug and thermally stable along the processing time. A required release profile is usually obtained by good selection of the polymer. The route of administration has to match with properties of selected polymer.

Solid lipids can be a carrier in hot-melt extrusion process. In order to extrude lipids, the process is operated at room temperature with/without applying some pressures or at temperature approximately 10°C below their melting points (Pinto and Silvério 2001; Reitz and Kleinebudde 2007; Krause et al. 2009). Polyglycolysed and fatty acid glycerides have been reported as a binder or a carrier for drug delivery systems prepared by hot-melt

extrusion (Reitz and Kleinebudde 2007). Thermal sensitive drugs can be incorporated into solid lipid extrusion due to no need of high extrusion temperature (Krause et al. 2009). As a carrier for drug delivery, solid lipids can also use as a bitter taste masking material or a solubilizing agent of lipophilic drugs (Reitz and Kleinebudde 2007). Although solid lipid stability is a problem of using them as carriers for drug delivery systems, some solid lipids have shown a good stability after hot-melt extrusion and promising drug release profiles after storage at elevated temperatures. Glyceryl trimyristate (Dynasan 114) is an example to demonstrate solid lipid stability. No change in polymorphic forms after hot-melt extrusion was observed. The drug release was similar before and after storage at 40°C until 9 months (Reitz and Kleinebudde 2007).

b) Plasticizers

Plasticizers are incorporated into polymers in order to principally reduce T_g and brittleness, adjust the mechanical properties, and improve the flexibility and workability of polymer (Wang et al. 1997; Brabander et al. 2002; Rahman and Brazel 2004). In general plasticizers seem to be small molecular liquids (Elias 2003).

Due to the benefits of plasticizers on polymers, they have been widely utilized in the process of hot-melt extrusion to improve the processibility of polymers (Repka et al. 1999; Zhu et al. 2006) and lower the extrusion temperatures (Wu and McGinity 2003; Zhu et al. 2006; Ghebremeskel et al. 2007; Verhoeven et al. 2008). For thermal labile drugs or ingredient such as peptides and proteins (Brange 2000), the decrease of processing temperatures by a plasticizer allows them to be fabricated using hot-melt extrusion. The processing temperatures above T_g are principally required to soften polymeric carriers enough to flow though a hot-melt extruder (Ghebremeskel et al. 2007). Therefore the decrease of melt viscosities and T_g with the addition of a plasticizer results in the reduction of extrusion temperatures.

Several plasticizers for hot-melt extrusion have been extensively investigated. Plasticizers with good efficiency, polymer-plasticizer compatibility and thermal stability are required (Crowley et al. 2007). Conventional plasticizers can also used. PEG, triethyl citrate and acetyltributyl citrate function as plasticizers for polymers, such as hydroxypropyl celloluse,

hydroxymethylpropyl cellulose and Eudragit®, to be able to process by hot-melt extrusion. They have an impact on physical properties, mechanical properties and drug release from hot-melt extrudates (Repka et al. 1999; Zhang and McGinity 1999; Repka and McGinity 2001; Zhu et al. 2006). For the process of hot-melt extrusion, a mixture of a polymer, a drug and other excipients needs to be physically mixed before adding into a hopper. A solid plasticizer provides ease for mixing and reduces a problem from evaporation of a liquid plasticizer when exposure to a high temperature (Wu and McGinity 2003). Therefore, a solid plasticizer is probably preferred. Methyl paraben, citric acid and some drugs, such as ibuprofen and chlorpheniramine maleate, have been reported to be a choice of solid plasticizers. The solid plasticizers help facilitate the process and suppress the T_g of the polymers (Zhu et al. 2002; Wu and McGinity 2003; Schilling et al. 2007). The functions as both a plasticizer and an active ingredient or an excipient increase their benefit to hot-melt extrusion.

c) Other excipient

Other excipient can be incorporated into a dosage form prepared by hot-melt extrusion. They aim to be a processing aid and/or a release modifier. A processing aid excipient is generally used to help hot-melt extrusion to process easily and efficiently. It has no or a little impact on properties of finish drug products. Glyceryl monostearate was investigated as a thermal lubricant. The addition of glyceryl monostearate into the blend of Eudragit® and the drug helped facilitate the thermal process. The decrease in the melt viscosity and the drag flow were observed without a change in T_g of the polymer (Zhu et al. 2004; Bruce et al. 2005). Carbon dioxide has been also reported to act as a molecular lubricant. An increase in free volume and a decrease in chain entanglement cause by the absorption of carbon dioxide between the polymer chains. The melt viscosity is secondly reduced due to the effect of lubricant (Verreck et al. 2006; Lyons et al. 2007).

A pore former is a release modifier for a dosage form prepared by hot-melt extrusion. A water-soluble material, for example sucrose, a salt (sodium chloride) or a water-soluble polymer (hydroxyl propyl cellulose and PEG), can be used as a pore former (Schilling et al. 2008; Özgüney et al. 2009; Douglas et al. 2010). It has normally higher water solubility than the materials, which are using as carriers and drugs (Chevalier et al. 2008). A pore former works to enhance drug releases by making pores, and thus an increase in drug diffusivity

through a porous extrudate. An appropriate release profile is simply achieved (Özgüney et al. 2009).

1.6. Release kinetics and mechanisms of biodegradable implants

The drug releases from biodegradable polymeric systems are controlled either by diffusion, degradation or a combination of both diffusion- and degradation-controlled mechanisms (Jain 2000). The combination of diffusion and degradation is the most common mechanism that can be found in scientific papers (Park et al. 1993; Fitzgerald and Corrigan 1996; Gallagher and Corrigan 2000; Zolnik et al. 2006).

The degradation-controlled mechanism happens when the diffusion rate of a drug is less than the degradation or erosion rate of a polymer carrier (Park et al. 1993). The drug is released tremendously at the same time as the polymer degradation. Sigmoidal release profiles are usually observed (Gallagher and Corrigan 2000; Berkland et al. 2002). As with the mechanisms of polymer erosion, drug release based on the degradation-controlled mechanism can be also divided into surface-degrading approach and bulk-degrading approach (Fitzgerald and Corrigan 1996; Karasulu et al. 2000).

For surface-degrading controlled mechanism, the surface-to-volume ratio and the geometry of implants have an impact on the drug release profiles. One of widely used model has been developed by Hopfenberg (1.1). The drug release depends on the erosion of polymer carrier. This model can be used for the matrices in slab, spherical and cylindrical shape and a drug has to be dispersed uniformly in the matrix (Park et al. 1993; Karasulu et al. 2000).

$$\frac{M_t}{M_\infty} = 1 - \left[1 - k_0 t / C_0 a_0\right]^n \qquad (1.1)$$

Where M_t is the amount of drug release at time t, M_∞ is the total drug release and k_0 is the erosion rate constant of the device. C_0 is the initial concentration of a drug in the matrix and a_0 is the initial radius of a sphere, cylinder or the half-thickness of a slab. The shape factor is represented by n: 1 for a slab, 2 for a cylinder and 3 for a sphere (Katzhendler et al. 1997; Karasulu et al. 2000).

Drug releases of PLGA- or PLA- based implants always relate to degradation of the polymer (Lao et al.; Santoveña et al. 2006). Since PLGA or PLA polymer undergoes bulk degradation (Jain 2000), drug release from this carrier is occasionally controlled only by bulk degradation-controlled release mechanism (Fitzgerald and Corrigan 1996). This equation can also be used to fit with the polymer erosion and to describe a part of drug release from PLGA drug delivery systems (Gallagher and Corrigan 2000).

$$\ln \frac{x}{(1 - x)} = kt + kt_{max} \qquad (1.2)$$

Where x is the fraction of drug released at time t, k is a rate constant and t_{max} is the time to maximum drug release rate (Gallagher and Corrigan 2000).

There are two widely used diffusion models for an explanation of diffusion-controlled release from matrices, Higuchi and Korsmeyer-Peppas model (Vueba et al. 2004; Avachat and Kotwal 2007; Kim et al. 2007). They also have been reported in the literature to explain mechanism of drug release from biodegradable implants when preparing in a matrix form (Park et al. 1993; Schliecker et al. 2004; Chang et al. 2005). Higuchi model can be applied when a drug is dispersed homogeneously in a polymer matrix. The relationship is as follows (Higuchi 1961; Kunou et al. 2000):

$$Q = \sqrt{D(2W - C_s) C_s t} \qquad (1.3)$$

Where Q is amount of drug released in time t, D is the drug diffusion coefficient in the matrix, C is the total drug amount per unit volume of matrix, C_s is the drug solubility and W is the total amount of drug per unit volume of matrix. When C >> Cs, the relationship can be shortened to the following equation:

$$Q = \sqrt{2DWC_s t} \qquad (1.4)$$

From the above equation, the amount of drug release is proportional to the square root of time. Therefore, it is possible to simplify the equation as follows (known as the simplified Higuchi model) (Costa and Sousa Lobo 2001):

$$Q = K_H t^{\frac{1}{2}} \quad (1.5)$$

In equation, K_H refers to Higuchi dissolution constant.

The Korsmeyer-Peppas is a model used for diffusion-controlled release (Schliecker et al. 2004). It is an exponential relationship between the amount drug release and the time. The portion of M_t/M_∞ is limited to less than 0.6 when using this model for fitting the curve of drug release (Korsmeyer et al. 1983; Costa and Sousa Lobo 2001). The equation is as follows:

$$\frac{M_t}{M_\infty} = kt^n \quad (1.6)$$

Where M_t is the drug released at time t, M_∞ is the quantity of drug release at infinite time and k is kinetic constant. For indicating Fickian diffussion, n is equal to 0.5 for a slab and 0.45 for a cylindrical shape (Korsmeyer et al. 1983; Costa and Sousa Lobo 2001).

The combination of degradation-controlled and diffusion-controlled release mechanisms occurs in drug release from matrices undergoing bulk degradation (Kunou et al. 2000; Alexis et al. 2004; Zolnik et al. 2006). The drug diffuses rapidly in comparison to the polymer degradation at the initial period. Then, the polymer degradation starts. The drug permeability and diffusivity increases with time (Kunou et al. 2000). The occurrence turns out to be difficult when writing this mechanism into an equation. A model by Baker for estimating the changing drug permeability with time and Higuchi model are combined (Park et al. 1993). The following equation is used to explain the mechanism regarding to both degradation-controlled and diffusion-controlled release.

$$M_t = A(2P_0e^{kt}C_0t)^{1/2} \quad (1.7)$$

Where M_t is the amount of released drug, P_0 is the drug permeability ($P_0 = DC_s$), and A is the total area of the matrix. C_0 and C_s are the drug concentration at the initial time and the drug solubility respectively. k is the first-order rate constant of bond cleavage of the polymer carrier (Park et al. 1993).

1.7. Methods to modify release profiles of biodegradable implants

A drug release profile from biodegradable implant normally shows bi- or triphasic release profile (Dorta et al. 2002; Desai et al. 2008). Starting with a burst release follows by a slow release or a constant drug release rate, and subsequently the last phase with a rapid release (Schliecker et al. 2004; Luan and Bodmeier 2006). A burst release is a drawback of monolithic implants. It may cause side effects due to rapidly increasing drug level in a short period of time (Huang and Brazel 2001). A burst release is undesirable for biodegradable implants. By contrast, a burst release can be a pharmaceutical benefit. It can be used as a loading dose for some drugs (Park et al. 2011) if an amount of a burst release can be reproducibility. Several methods to modify release profiles have been reported in literatures. The following review includes the methods associated to either biodegradable monolithic implants, microparticles or in situ implants in order to achieve desired a release profile from biodegradable implants.

1.7.1. Effect of additives

The addition of a biocompatible material can modify the drug release from biodegradable implants (Desai et al. 2008). It can have a big effect on drug release manners, even on release mechanisms. The choice of additives for biodegradable implants is limited by toxicity and biocompatibility, since they are administered parenterally into the body. Biocompatible materials are an appropriate option to be considered.

Polyethylene glycol (PEG) is a well-known pharmaceutical excipient and has been conventionally used as a plasticizer, solvent or solubilizing agent (Johnson et al. 1991;

Schade et al. 1995; Rowe et al. 2003; Strickley 2004; Pongjanyakul and Puttipipatkhachorn 2007; Srinivasa et al. 2007). PEG is a water soluble polymer. For solid dispersion, PEG has been widely incorporated into this kind of dosage form in order to enhance the drug solubility (Verheyen et al. 2002; Urbanetz and Lippold 2005). PEG can be also found in the formulations of some parenteral commercial products, such as Depo-Provera® (a contraceptive injection) due to approval by the U.S. Food and Drug administration for parenteral use in human (Zhu et al. 1990). PEG has been extensively investigated as a plasticizer for PLA and PLGA, especially L-PLA. The plasticizing effect of PEG on PLA extrudates has demonstrated to reduce T_g, transform PLA from brittle to ductile behavior and improve mechanical properties of the polymer (Jacobsen and Fritz 1999; Baiardo et al. 2003; Pillin et al. 2006; Piorkowska et al. 2006). Ease of fabrication can be reach with the presence of PEG in PLA. For PLGA, PEG was added into films prepared by solvent casting for drug delivery. The previous studies showed only the reduction of T_g and change in degradation of PLGA (Schade et al. 1995; Tan et al. 2004). The presence of PEG in formula of PLGA- or PLA- based implants has also an impact on drug release profiles (Tan et al. 2004; Steele et al. 2011). It could either increase or decrease in drug releases. Besides T_g of PLGA and PLA are reduced by PEG, a decrease in the initial release was reported when PEG has been added into PLGA and PLA matrix systems. The initial burst was suppressed without any changes in the drug release profiles. More hydrophilicity of the plasticized polymer helps reduce in the initial burst release for hydrophilic drugs (Tan et al. 2004; Tang and Singh 2008). By contrast, the addition of PEG can enhance a release of a drug. When crystalline PEG (high molecular weight PEG) is dispersed in PLGA or PLA matrix, it can act as a pore former. PEG leach out from the matrix and a drug can easily release through the pores created by dissolved PEG (Steele et al. 2011).

Additives have also an influence on PLGA- or PLA- based implants (Zhu and Schwendeman 2000; Desai et al. 2008; Park et al. 2011). Two main purposes of adding an excipient have been explored. Firstly, a continuous drug release without a lag time phase is required. Another is to stabilize an incorporating drug, which is typically a therapeutic protein. A release profile can be modified by the addition of a pore former in the form of metal salt, an oligomer of the polymers, and a plasticizer (Hu et al.; Géze et al. 1999). A plasticizer can reduce an initial burst release (Tan et al. 2004; Tang and Singh 2008). A material, which can create pores, increase drug releases due to drug diffusion through the pores. For example, a

continuous drug release could achieve by the addition of $MgCO_3$ as a pore former. PLA oligomers showed either an increase or a decrease in the drug releases (Desai et al. 2008). The small oligomers with molecular weight about 800 created the larger amount of the initial drug release, whereas the incorporation of the longer chain oligomers (molecular weight = 1100) resulted into a continuous prolonged release (Géze et al. 1999). A therapeutic polypeptide or protein can be stabilized by the addition of an additive (Meinel et al. 2001; Kang and Schwendeman 2002). Due to acidic microclimate of PLGA- or PLA-based implants after degradation, the stability of polypeptides or protein seems to be an issue. An incorporation of a basic inorganic salt as $Mg(OH)_2$ improved the stability of a model protein, which is bovine serum albumin. Aggregation of bovine serum albumin was decreased with an increase in the amount of $Mg(OH)_2$ (Zhu and Schwendeman 2000; Kang and Schwendeman 2002).

1.7.2. Coating

There are many methods to coat the biodegradable monolithic implants. The methods are mostly solvent associated methods. PLGA or PLA is firstly casted into a film using an organic solvent or is dissolved in an organic solvent. The film is used to wrap a biodegradable implant by the aid of heat compression (Qian et al. 2002; Kim et al. 2008) and the polymer solution is used as a coating solution. A biodegradable implant is then dipped into the polymer solution. The coating layer on the implant is formed upon the solvent evaporation. This method is called dip coating method, which can be used to produce coated PLGA- or PLA-based implants on a small scale (Wang et al. 1996; Sebree and Siegel 2008).

Coated PLGA- or PLA-based implant is a useful device to control drug releases, particularly for low molecular weight drugs with high water solubility (Zhang et al. 1994; Zhang et al. 1995). Coating can slow down a drug release rate and alter drug release profiles of PLGA- or PLA- based biodegradable implants. It can be a potential method to reduce an initial burst release from PLGA- or PLA-based implants (Negrín et al. 2004; Kovalchuk et al. 2005; Sebree and Siegel 2008). A sustained release or zero-order release profile can be achieved (Wang et al. 1996; Qian et al. 2002).

1.7.3. Polymer blends

Polymer blend is a result from a physical mixing of two or more polymers. The purposes of polymer blend are to prepare a new material for meeting requirements in several applications, combine the positive features of different materials and to avoid the disadvantages of each polymer (Bae and Kim 1993; DeMeuse 1995; Domb et al. 1999). The advantages of polymer blends for controlled release applications are easy fabrication, improvement of properties (such as hydration, mechanical strength, degradation rate, drug release) and an increase in drug loading (Bae and Kim 1993).

In the field of plastics the polymer blends can be achieved by four processes, which are melting mixing, solution blending, latex blends and in situ polymerization (Elias 2003). Three of them (melting mixing, solution blending and latex blending) have been focused in the area of pharmaceutical science. Melting mixing, for example hot-melt extrusion, is a process involving heat and mixing. Two polymers are molten at an elevated temperature and then they are mixed to form a polymer blend (Nieminen and Oy 2007). For solution blending, two polymers are separately dissolved into suitable solvents. Two polymer solutions are poured together into a container with vigorous agitation. A blend is obtained after evaporation of the solvent (Shundo et al. 1966). Another method is latex blending. By this method two aqueous polymer dispersions are mixed. The blends obtain when coagulation occurs (Elias 2003).

Miscibility of polymer blend is basically classified into miscible and immiscible blends. A miscible polymer blend is a single phase material (DeMeuse 1995). A T_g can be detected when using differential scanning calorimetry (DSC). Using this analytical technique, less than 20 nm particles from phase separation cannot be determined (Pillin et al. 2006). A single T_g is assumed as a mixing at molecular level of polymer blends. By contrast, an immisible blend is heterogeneous and composes of two or more phases. Two or more T_g have been observed for immiscible blends. Two distinct T_g from immiscible polymer blends display generally in the same temperature as T_g of the individual polymer (Jorda and Wilkes 1988; Cameron et al. 2002; Pillin et al. 2006). In addition to two distinct T_g, two separated phases or polymer emulsion occur when polymers are immiscible (Roths et al. 2002; Lipatov 2006).

Several theoretical and empirical equations have been used to estimate T_g of miscible polymer blends. A widely used equation for predicting T_g of blend system is Gordon-Taylor equation (Katkov and Levine 2004). T_g of the blend system can be calculated using the equation as followed:

$$T_g\,(K) = \frac{W_1 T_{g1} + kW_2 T_{g2}}{W_1 + kW_2} \tag{1.8}$$

W_1 and W_2 are the weight fraction and T_{g1} and T_{g2} represent T_g value of each component. The Gordon-Taylor coefficient (k) was originally based on polymer free volume theory. The simple equation has been afterward established including the true density in order to achieve k (Katkov and Levine 2004).

$$k = \frac{\rho_1 T_{g1}}{\rho_2 T_{g2}} \tag{1.9}$$

Another equation for the prediction of T_g of a polymer system is Fox equation (Fox 1956). It has been widely used when the system is compatible and weak interaction is observed (Pillin et al. 2006). The equation is as followed:

$$\frac{1}{T_g} = \frac{W_1}{T_{g1}} + \frac{W_2}{T_{g2}} \tag{1.10}$$

T_{g1} and T_{g2} refer to T_g of a pure polymer or an additive in Kelvin, whereas W_1 and W_2 are the weight fraction of each composition.

The better properties from polymer blends compared to a polymer itself can be useful for drug delivery systems as drug carriers (Domb et al. 1999). For biodegradable implants, blends of different molecular weight of PLGA or PLA polymer are the first method to obtain a continuous release from the implants. This finding has been explained by two possible explanations. The lower molecular weight of the biodegradable polymers degrades faster and leaves the matrix resulting into pore formation. Secondly, an increase in hydrophilic carboxyl groups during the polymer degradation leads to more hydrophilicity of the matrix. It enhances

water uptake of the system. In combination of two occurrences a drug release from blends of different molecular weight of PLGA or PLA shows smooth and continuous release profiles (Wischke and Schwendeman 2008). A continuous release from PLGA- or PLA-based implants prepared by hot-melt extrusion is obtained when blending two PLGA or PLGA and PLA with different molecular weight. Coating is not necessary to reduce an initial burst. These blending methods are useful for relesase of peptides, analgesic-narcotic drugs and steroid hormones (Mauriac and Marion 2008). The drug release also depends on the ratio of amount of the polymer with different molecular weight. When an optimal ratio is reached, the most smooth and continuous drug release is observed (Kunou et al. 2000).

1.8. In vitro and in vivo drug release study for implants

Several concerns are taken into consideration when perform a test for in vitro drug release of implant drug delivery system. Due to a long duration of a drug release from an implant, the evaporation of the release medium and the microbial contamination should be prevented. A preservative, such as benzalkonium chloride or sodium azide, has been added into a release medium. The osmolarity, pH, buffer capacity, volume and composition of the release medium, which is chosen for the in vitro drug release, play a role in the drug release. They normally assume to represent the condition of plasma or the physiological fluid. Following on starting of the drug release test, the drug concentration increases as a function of time in the release medium. In some cases, a sink condition (an excess solubility capacity of the release medium or the drug concentration in the release medium less than one-third of the drug solubility) is considered. Another attention should play on the predetermined time points for sampling. An appropriate interval is necessary to characterize correctly a release profile. While too long sampling interval can lead to misunderstand drug release manners from implants, excessively frequent sampling is a waste of time. Moreover, the stability of active ingredients or drugs in the release medium is important. A drug has to be stable in the in vitro condition at the determined temperature and at pH of the release medium along the in vitro drug release test (Stiewert et al. 2003; Iyer et al. 2006).

Several methods have been used to determine in vitro drug releases from implant drug delivery systems. The compendial apparatus 4 device (Flow-Through Cell) is only equipment, which has been recommended on FIP/AAPS Guideline for drug release testing of implants

(Iyer et al. 2006). The apparatus consists of a flow-through cell, a pump and a water bath to maintain the release medium at 37 ± 0.5 °C. The standard flow rates as recommended in the USP are 4, 8 and 16 ml/min. The flow-through cell is made from transparent and inert materials and built to the vertical setting. During the test, the critical parameters including volume, temperature and flow rate of a medium have to be monitored and controlled (United States Pharmacopeial Convention 2006). The dissolution or drug release study of implants in a compendial viewpoint using USP apparatus 4 is usually desirable, but it is sometimes impractical (Iyer et al. 2006). A large amount of a medium is used in comparison with the traditional shaking method, because the real time study of implants always takes more than a month. Although a receptor compartment of USP apparatus 4 tries to mimic the in vivo condition, placing an implant in direct contact with a release medium is the weakness of the flow-through cell.

A widely utilizing method from the literatures for implants is the shaking method (Schmidt et al. 1995; Kunou et al. 2000; Eperon et al. 2008; Tang and Singh 2009). A vial, a tube or a flask containing a release medium is placed into a shaker. At determined time points small amount of the release medium is withdrawn and measured a drug concentration (Iyer et al. 2006). This method uses agitation to reduce the boundary layer of the drug release. The drug concentration is homogeneous though out the release container. One concern regarding to this method is appropriate volume of a release medium. It relates to the term of sink condition. A sink condition is an excess solubilizing capacity of a release medium (Rohrs 2001) or a condition that a drug concentration remains below saturation (Iyer et al. 2006). Under the sink condition the drug concentration in a release medium does not affect the release or drug delivery. Therefore, a sink condition is necessary for the shaking method. A sufficient volume of a release medium should be put into a shaking container with regard to maintain a sink condition.

The subcutaneous layer is the deepest layer of skin beneath epidermis and dermis (Xu et al. 2008). Subcutaneous implantation refers to the method by which drugs are implanted into adipose and connective tissues under dermis layer of skin (Sankaram 2000). Therefore, an implant is usually surrounded by the body tissues concerning to the in vivo condition at the site of implantation. Different phenomena occur comparing to in vitro release study that placed an implant directly into a release medium. Therefore, some modified release media

and special conditions have been explored based on in vivo environment. Gel methods using agar and agarose as release media were reported. Agar was selected to simulate subcutaneous tissues according to viscosity, water content and the composition of the intracellular matrix of subcutaneous tissues, which compose of collagen, polysaccharides and water. No significant difference between using agar release method and vial method fulfilled with 0.1 M phosphate buffer pH 7.4 was found for the drug release from glyceryl monosterate-based implants due to the high solubility in water of the used model drug (Allababidi and Shah 1998). By contrast, using agarose to mimic a living tissue condition demonstrated the faster drug release from PLGA-based microparticles in comparison to the release study using the agitated test tubes containing phosphate buffer pH 7.4. More difficulty of the acid by-product's difussion from PLGA degradation in agarose was a reason of this observation. The system degraded more rapidly because of the autocatalytic effect resulting to the faster drug release (Klose et al. 2008).

The real-time in vitro release study of prolonged drug release implants is time-consuming. It has to be performed along a period of several weeks to months depending on the designed duration of action. An accelerated in vitro release study is a resolution to overcome this trouble. It assists in the early state of product development to discriminate formulations. Changes in conditions for in vitro release study can accelerate drug release profiles. Various parameters including temperature, ionic strength, pH, surfactants and agitation rate can be modified (Iyer et al. 2006). For biodegradable implants, every factor that enhances degradation of polymer carriers can increase release rates. An increase in temperature for biodegradable implants resulted into a faster drug release. The release rate increases with an increase in the temperature from 37°C up to 60°C. The drug release at elevated temperatures could be correlated with the real-time drug release. This finding is helpful to predict a real-time drug release of biodegradable implants in a short period of time (Shameem et al. 1999; Iyer et al. 2007). Moreover, in a stress condition for accelerated drug release, either elevated temperature, an addition of a surfactant or critical pH, the stability of implants and drugs have to be taken into consideration. They must be chemically and therapeutically stable along the stress in vitro drug release test (Iyer et al. 2007).

1.9. Objectives

The aim of this study was to develop and to characterize biodegradable implants based on PLGA or PLA polymer with controlled release manners for parenteral drug delivery systems. The particular purposes were as follows:

a) To achieve drug release profiles with different release patterns and mechanisms.
b) To optimize the processes for preparing biodegradable PLGA or PLA implants.
c) To investigate key parameters influencing on physical, thermal properties and drug release profiles of biodegradable PLGA or PLA implants.
d) To determine the effect of some additives or polymer blends on the properties of biodegradable PLGA or PLA implants and drug releases.
e) To simulate in vivo condition for testing drug release study of biodegradable PLGA implants.

Several small molecular weight model drugs with different aqueous solubility and lipophilicity were incorporated into the biodegradable implants. The implants were prepared by compression, coating and hot-melt extrusion method.

2. Materials and Methods

2.1. Materials

The following chemical substances were used as received:

Model drugs

Tramadol hydrochloride (tramadol HCl) (Heumann Pharma GmbH & Co. Generica KG, Nuernberg, Germany)
Dexamethasone sodium phosphate (dexamethasone salt) (CHEMOS GmbH, Regenstaut, Germany)
Theophylline (BASF AG, Ludwigshafen, Germany)
Ibuprofen (BASF AG, Ludwigshafen, Germany)
Diazepam (Kraemer & Martin GmbH, Sankt Augustin, Germany)

Table 2.1. Melting points and solubility of model drugs in phosphate buffer pH 7.4 containing 0.01% w/v sodium azide

Drugs	Drug solubility (mg/ml)	Melting point (°C)
Tramadol HCl	793.5 ± 97.8 [(a)]	171 – 173 [(1)]
Dexamethasone salt	433.2 ± 13.7 [(a)]	224 – 229
Theophylline	12.7 ± 0.7 [(b)]	270 – 274 [(2)]
Ibuprofen	7.0 ± 0.1 [(b)]	78 – 80 [(3)]
Diazepam	0.2 ± 0.02 [(b,c)]	131 – 136

[(a)] = at room temperature; [(b)] = at 37°C; [(c)] = with the addition of 0.1% w/v SDS

[(1)] (Buschmann et al. 1998)

[(2)] (Zelkó and Süvegh 2005)

[(3)] (Kidokoro et al. 2001)

Polymers

Poly (lactide-co-glycolide) (PLGA) Resomer® RG 502H; PLGA Resomer® RG 503H (Boehringer Ingelheim Pharma GmbH & Co. KG, Ingelheim, Germany)
Poly (D,L-lactide) (PLA) Resomer® R 202H (Boehringer Ingelheim Pharma GmbH & Co. KG, Ingelheim, Germany)

Table 2.2. Inherent viscosity of PLGA and PLA

Polymers	Inherent viscosity (dl/g) [1]
PLGA RG 502H	0.16 – 0.24
PLGA RG 503H	0.32 – 0.44
PLA R 202H	0.16 – 0.24

[1] Obtained from the measurement of 0.1% solution in chloroform at 25°C and provided by Boehringer Ingelheim Pharma GmbH & Co. KG, Ingelheim, Germany

Polyethylene glycols (PEG) MW 400, 1500 and 4000 (Lutrol E 400, 1500, 3350 and 4000) (BASF AG, Ludwigshafen, Germany); PEG 3350 (Carbowax 3350, The Dow Chemical Company, Midland, United States)

Solid lipid (Long chain triglycerides)

Tripalmitin (Dynasan 116), tristearin (Dynasan 118) (Condea Chemie GmbH, Witten, Germany)

Other additives

Magnesium hydroxide (Fluka, Buchs, Switzerland)
Sodium Chloride (Merck KGaA, Darmstadt, Germany)

Solvents

Methylene chloride, dimethyl sulfoxide (Merck KGaA, Darmstadt, Germany)
Glycerin (Carl ROTH GmbH, Karlsruhe, Germany)
Medium chain triglyceride (MCT) (Miglyol 812 N®, Synopharm GmbH, Barsbüttel, Germany)
Soybean oil (Sigma-Aldrich Chemie GmbH, Steinheim, Germany).

Release media

Phosphate buffer pH 7.4 USP (50 mM) with 0.01% w/v sodium azide composed of Potassium dihydrogen phosphate, disodium hydrogen phosphate, sodium hydroxide and sodium azide (Merck KGaA, Darmstadt, Germany)
Lipofundin^{TM} (the formula shows in Table 2.3)

Table 2.3. Formula of MCT/ LCT 20%w/v

Ingredient	Amount
Soybean oil (LCT)	100 g
Coconut oil (MCT)	100 g
Egg yolk lecithin	12 g
Glycerin	25 g
α-Tocopherol	0.2 g
Sodium oleate	0.3 g
Water for injection qs to	1000 ml

2.2. Methods

2.2.1. Preparation of implants

a) Compression

PLGA and 10% w/w (percentage based on polymer) theophylline or dexamethasone salt were premixed using mortar and pestle. The punch and die set (2 mm in diameter with the concave surface) was used to prepare the implants. The mixture approximately 10 mg was filled manually into the die. The direct compression was performed by Instron testing instrument (Instron 4466, Instron Deutschland GmbH, Pfungstadt, Germany). Processing parameters were as follows: upper punch speed, 2.54 mm/min; compression force, 1 KN; holding time after the compression, 1 min.

b) Hot-melt extrusion

All ingredients were premixed physically by using mortar and pestle. An additive (tristearin or PEG) or another biodegradable polymer for a polymer blend was added into PLGA or PLA polymer before addition of a model drug. The mixtures were fed through a hopper and then extruded using a twin-screw hot-melt extruder (Minilab HAAKE Rheomex CTW5, Thermo Scientific, Karlsruhe, Germany). Processing parameters were as follows; extrusion temperatures, 65-100°C; screw speed, 20 rpm; die diameter, 1-1.75 mm.

c) Dip coating

Dip coating technique was applied for coating PLGA implants by using either biodegradable polymer or tripalmitin as coating materials. For implants prepared by hot-melt extrusion, extrudates were manually cut into the length of 5 mm before dip coating. The implant (either hot-melt extrudates or the implant prepared by compression) was handled by a pin and a holder. It was then dipped into PLGA or PLA solution (200 mg/ml in methylene chloride) for 2 second and subsequently turned upside down. The implants were dried by two consecutive steps: under a hood for 24 h, and at 40°C in a hot air oven for 4 h. For tripalmitin coating, tripalmitin was melted firstly by heating to about 75°C (10°C above its melting temperature).

The cores were dipped into molten tripalmitin for 2 sec. The coated implants were cooled down at the ambient condition. After dip coating, the implants were turned upside down to spread the coating solution before the coating layer was dried or solidified.

$$\text{Weight gain (\%)} = \frac{\text{Weight after coating - Initial weight}}{\text{Initial weight}} \times 100 \qquad (2.1)$$

2.2.2. Measurement of melt viscosity

The melt viscosity as a representation of torque values was observed directly during the hot-melt extrusion process (extrusion temperature, 65 - 100°C; screw speed, 20 rpm). The amount of each mixture was controlled equally (5 g). Torque values were recorded continuously and the maximum values were determined.

2.2.3. Determination of mechanical properties

Mechanical properties (tensile strength and elongation at break) were studied using a texture analyzer (TA.XT plus, Winopal Forschunungsbedarf GmbH, Ahnsbeck, Germany). The diameter and the length (L_o) of each hot-melt extrudate were measured and the surface area (A) was calculated before the test. The extrudate was pulled at a speed of 2.54 mm/s. The force in tension and the change in distance (ΔL) were recorded until each extrudate was broken.

$$\text{Tensile strength (psi)} = \frac{\text{Force at break (N)}}{\text{Area of cross section (m}^2\text{)}} \qquad (2.2)$$

$$\text{Elongation at break (\%)} = \frac{\Delta L}{L_o} \times 100 \qquad (2.3)$$

2.2.4. Differential scanning calorimetry (DSC)

Thermal properties of samples were studied using differential scanning calorimetry (DSC) (Mettler DSC 821^e, Mettler Toledo, Giessen, Germany). Hot-melt extrudates were cut

manually into small pieces. The sample (5-10 mg) was weighed accurately in a 40 µl aluminum crucible and then closed with a cover. All tests were run under a nitrogen atmosphere at scanning rates: heating 10°C/min over a temperature range of -20 to 150°C and cooling 15°C/min over a temperature range of 150 to -20°C, and cycled twice. A glass transition temperature (T_g) and a melting point (T_m) were derived from the thermograms using STAR® software (Mettler Toledo, Giessen, Germany). Quantitative analysis of PEG solubility upon storage was adapted by the calorimetric method. The calculation based on heat of fusion (j/g) of its crystalline peak (Gray 1970).

To study the effect of each ingredient of Lipofundin on T_g of PLGA, PLGA 502H was immersed into 25% w/v solution of each ingredient in methanol and then shaken overnight at room temperature. The samples were dried using a vacuum oven (Heraeus VT 5042 EK, Heraeus Holding GmbH, Hanau, Germany) for 24 h. A similar method and apparatus as described above were used.

2.2.5. Thermogravimetric analysis (TGA)

Thermal stability of PLGA and PLA was studied using thermogravimetric analysis. A sample (approximately 5 - 15 mg) was placed in a porcelain crucible. Change in weight was measured using Mettler TC 15-TA controller coupled with a Mettler TG 50 thermobalance (Mettler Toledo AG, Giessen, Germany) during heating 10°C/min from 30-500°C. The mass remaining was calculated by the following equation:

$$\text{Mass remaining}\,(\%) = \frac{\text{Final weight}}{\text{Initial weight}} \times 100 \qquad (2.4)$$

2.2.6. Powder X-ray diffraction

Hot-melt extrudates were ground into small particles before the test. Measurements were performed on a Philips PW 1830 X-ray generator with a copper anode (Cu Kα radiation, λ = 0.15418 nm, 40 kV, 20 mA) fixed with a Philips PW 1710 diffractometer (Philips Industrial & Electro-acoustic Systems Division, Almelo, The Netherlands). The scattered radiation of the samples was detected with a vertical goniometer (Philips PW 1820, Philips Industrial &

Electro-acoustic Systems Division, Almelo, The Netherlands). A scanning rate of 0.02° 2θ per sec over the range of 4-40° 2θ at ambient temperature was used to determine each spectrum.

2.2.7. Drug release study

a) Bottle method

Implants (5 mm hot-melt extrudates or implants prepared by compression) were accurately weighed. Each samples (tramadol HCl, 4 implants; dexamethasone salt 2 implants; other model drugs, 1 implant) was immersed in a 50 ml glass bottle (n=3) containing 50 ml phosphate buffer pH 7.4 USP (50 mM) with 0.01% w/v sodium azide as a preservative. For release studies of diazepam implants, 0.1% w/v sodium dodecyl sulfate (SDS) was added into the buffer in order to maintain sink condition. The bottles were incubated in a horizontal incubation shaker (GFL 3033, Gesellshcaft für Labortechnik GmbH & Co. KG, Burgwedel, Germany) at 37°C, 70 rpm. At predetermined time points, 2 ml release medium was withdrawn (no medium replacement). The drug concentration was analyzed by UV spectrophotometry (UV-visible scanning spectrophotometer 2101 PC, Shimadzu Scientific Instruments, Columbia, MD, USA) at the wavelength of 271 nm for tramadol HCl, 242 nm for dexamethasone salt, 272 nm for theophylline, 264.6 nm for ibuprofen and 250 nm for diazepam.

Remaining drug was quantitatively detected after the drug release studies were terminated. The implants were taken out from the release medium and dried by vacuum oven (Heraeus oven VT 5042 EKP, Hanau, Germany coupled with a chemistry hybrid pump, Vacuubrand GmbH, Wertheim,Germany) for 4 h. Approximately 4 ml of 1.0 N NaOH was added to a vial containing the dried implant. The vial was then shaken at room temperature (200 rpm) until the dried implant was completely dissolved. The solution was adjusted to 5 ml volume by 1.0 N NaOH. The resulting solution was further diluted 1:1 or 1:3 using water in order to obtain an appropriate UV absorbance for drug analysis. The final solution was analyzed by UV spectrophotometry at the wavelength mentioned above.

b) Tube method (for simulating in vivo study)

For simulating in vivo subcutaneous condition, diluted Lipofundin (1:4) and phosphate buffer pH 7.4 USP containing 0.01% w/v sodium azide and 0.1% w/v SDS were used as release media. 10% w/w diazepam implant was immersed into 10 ml release medium and incubated under the similar condition as described above. All samples were run in triplicate. At the fixed time interval, the implant was withdrawn and dried using the vacuum oven overnight. The dried implant was then dissolved in dimethyl sulfoxide and the remaining drug concentration was analyzed by UV spectrometry at $\lambda = 250$ nm.

2.2.8. Water uptake, mass loss and mass remaining study

Water uptake, mass loss and mass remaining study were determined gravimetrically using Mettler M3 microbalance (Mettler Toledo, Gießen, Germany) under the similar release medium and condition as prescribed above for the drug release study. Firstly, an implant was weighed accurately (Initial weight). Each sample was immersed separately into the release medium. All samples were run in triplicate. At fixed time intervals, the samples were taken out, wiped with tissue paper to remove excess water, and finally weighed (Wet weight). The samples were then dried under vacuum in an oven (Heraeus oven VT 5042 EKP, Hanau, Germany coupled with a chemistry hybrid pump, Vacuubrand GmbH, Wertheim,Germany) overnight and subsequently in a desiccator until constant dry weight (Dry weight) was reached. Water uptake, mass loss and mass remaining were calculated by the following equations:

$$\text{Water uptake}\,(\%) = \frac{\text{Wet weight - Dry weight}}{\text{Dry weight}} \times 100 \qquad (2.5)$$

$$\text{Mass loss}\,(\%) = \frac{\text{Initial weight - Dry weight}}{\text{Initial weight}} \times 100 \qquad (2.6)$$

$$\text{Mass remaining}\,(\%) = \frac{\text{Dry weight}}{\text{Initial weight}} \times 100 \qquad (2.7)$$

2.2.9. Optical light macroscope

Rupturing behavior of coated PLGA implants and implant morphology were studied using a macroscope (Inteq Informationstechnik GmbH, Berlin, Germany). The implant after incubation under the same condition as in the drug release study was withdrawn at the predetermined time point. The implant was observed immediately. The magnification of macroscope was adjusted until a clear observation was reached. The morphology was recorded by image analysis software (EasyMeasure, Inteq Informationstechnik GmbH, Berlin, Germany).

2.2.10. Scanning electron microscope (SEM)

Scanning electron microscope (SEM) was used to observe interior morphology at cross section of hot-melt extrudates. Firstly, hot-melt extrudates were cut into approximately 3-5 mm pieces. The samples were subsequently sputtered under an argon atmosphere with gold to a thickness of 8 nm (SCD 040, Bal-Tec GmbH, Witten, Germany), and observed using a scanning electron microscope (S-4000, Hitachi High-Technologies Europe GmbH, Krefeld, Germany)

2.2.11. Determination of octanol/water partition coefficient (log $K_{o/w}$) of drugs

Octanol/water partition coefficients of the model drugs were determined using a shake flask technique (Takács-Novák and Avdeef 1996). Octanol was pre-saturated with deionized water for 24 h before use. A model drug (tramadol HCl or dexamethasone salt) was dissolved into deionized water in certain concentration. 20 ml of n-octanol and the water phase containing the drug were added into a flask. The flask was placed on the shaker at ambient temperature, 100 rpm. Intensive shaking for 4 h was performed to reach equilibrium. Then, after phase separation the drug concentrations were analyzed spectrophotometrically (UV-visible scanning spectrophotometer 2101 PC, Shimadzu Scientific Instruments, Columbia, MD, USA; at λ = 271, 242 and 250 nm for tramadol HCl and dexamethasone salt, respectively). log $K_{o/w}$ was calculated by the following equation:

$$\log K_{o/w} = \log \frac{C_0}{C_w} \quad (2.8)$$

Where C_0 is the drug concentration in n-octanol and C_w is the drug concentration in the water phase.

2.2.12. Determination of apparent partition coefficient (K_{app}) of drugs

PLGA implants were immersed into 25 ml release medium (phosphate buffer pH 7.4 USP containing 0.01% w/v sodium azide) for 24 h. The wet weight (W) of the implant was measured. Then, the wet implant was immersed into 25 ml diazepam solution in the release medium (concentration, approximately 12 μg/ml) and incubated at 37°C, 70 rpm using a horizontal incubation shaker (GFL 3033, Gesellshcaft für Labortechnik GmbH & Co. KG, Burgwedel, Germany). The drug concentrations of diazepam solution at initial and time t were determined. K_{app} of diazepam between the release medium and the implant was calculated as followed:

$$K_{app} = \frac{C_0 - C_t}{W \cdot A \cdot C_t} \quad (2.9)$$

The equation (2) was modified from the equation of Miyajima et al (Miyajima et al. 1998). In the equation, A is the surface area/volume ratio of an implant; W is a wet weight of implant; C_0 and C_t are drug concentrations at the initial and time t.

2.2.13. Determination of drug diffusivity

PLGA and tripalmitin films containing 5% w/w theophylline (based on the polymer) were prepared in order to calculate theophylline diffusivity through PLGA and tripalmitin films. PLGA or tripalmitin and theophylline were physically mixed with a mortar and pestle. PLGA films were prepared by solvent casting technique. The physical mixture was dissolved in methylene chloride at a concentration of 10% w/w. The solution was then cast into a small Petri dish (30 mm in diameter). The solvent was evaporated under a hood at ambient condition for 2 days. Tripalmitin film was obtained by melt casting method. The physical

mixture was molten by heating at 75°C and cast into the Petri dish. Triplamitin film was cooled at ambient condition to room temperature. Film thickness was measured using Minitest 600 (Erichsen GmbH & Co KG, Hemer, Germany). Each film was immersed into 100 ml phosphate buffer pH 7.4 USP containing 0.01% w/v sodium azide in a 100 ml glass bottle. The bottle was incubated at 37°C and shaken in a horizontal incubation shaker at 70 rpm. The experiment was run in triplicate. Drug release at the predetermined time points was analyzed spectrophotometrically at the wavelength of 272 nm. Drug release fraction (M_t/M_∞) was plotted against the square root of time ($t^{1/2}$) and the slope was determined.

$$\frac{M_t}{M_\infty} = 4\left[\frac{Dt}{\pi l^2}\right]^{1/2} \tag{2.10}$$

$$\text{Slope} = 4\left[\frac{D}{\pi l^2}\right]^{1/2} \tag{2.11}$$

Where M_t is the drug released at time t, M_∞ is the quantity of drug release at infinite time, l is the thickness of film and D refers to drug diffusivity (Ritger and Peppas 1987)

2.2.14. Drug solubility study

Excess amount of the model drug (tramadol HCl, dexamethasone salt, theophylline, ibuprofen and diazepam) was placed into 3 ml phosphate buffer pH 7.4 USP. For diazepam, 0.1% w/v SDS was added to enhance the drug solubility. The experiment was run in duplicate. The samples were then incubated for at least 48 h until reach the equilibrium (the drug concentration was constant) at 37 °C or at room temperature for tramadol HCl and dexamethasone salt, 70 rpm using the horizontal incubation shaker. The final pH of the saturated solution was adjusted to pH 7.4. The saturated drug solution was subsequently filtered through a filter needle, and immediately diluted. The drug solution was diluted more to achieve an appropriate concentration for analysis using spectrophotometry. The drug concentration was measured by UV-VIS spectrophotometer at the wavelength of 271, 242, 272, 264.6 and 250 nm for tramadol HCl, dexamethasone salt, theophylline, dexamethasone salt and diazepam respectively.

2.2.15. pH measurement

At the determined time points, the implants after incubation under the similar condition as the drug release study were blotted using tissue papers and subsequently ground. 2 ml of distilled water was added to the crushed implant. The pH of suspension containing the particles from the implant was measured wiht a pH meter (Sartorius Basic Meter, Sartorius AG, Goettingen, Germany).

2.2.16. Mathematical models and equations

Three theoretical equations were used to explain the drug release from PLGA /tristearin implants prepared by hot-melt extrusion. Eq. (5) was described as a degradation-controlled mechanism (Gallagher and Corrigan 2000):

$$\ln \frac{x}{(1 - x)} = kt + kt_{max} \qquad (2.12)$$

Where x is the fraction of drug released at time t, k is a rate constant and t_{max} is the time to maximum drug release rate.

The Korsmeyer-Peppas model was used for diffusion-controlled release (Korsmeyer et al. 1983):

$$\frac{M_t}{M_\infty} = kt^n \qquad (2.13)$$

Where M_t is the drug released at time t, M_∞ is the quantity of drug release at infinite time and k is kinetic constant. For cylindrical shape, n equal to 0.45 indicates a diffusion-controlled mechanism.

Another equation to describe a diffusion-controlled release mechanism is the Higuchi model. Higuchi model was applied when a drug is dispersed homogeneously in a polymer matrix. The relationship was displayed as follows (Higuchi 1961; Kunou et al. 2000):

$$Q = \sqrt{D(2W - C_s) C_s t} \quad (2.14)$$

Where Q is amount of drug released in time t, D is the drug diffusion coefficient in the matrix, C is the total drug amount per unit volume of matrix, C_s is the drug solubility and W is the total amount of drug per unit volume of matrix. When C >> Cs, the relationship can be shortened to the following equation:

$$Q = \sqrt{2DWC_s t} \quad (2.15)$$

From the above equation, the amount of drug release is proportional to the square root of time. Therefore, it is possible to simplify the equation as followed (known as the simplified Higuchi model:

$$Q = K_H t^{\frac{1}{2}} \quad (2.16)$$

In equation, K_H refers to Higuchi dissolution constant.

3. Results and Discussion

3.1. Pulsatile release pattern from PLGA implants prepared by direct compression

3.1.1. Introduction

Poly(lactide-co-glycolide) (PLGA) has been fabricated into time-controlled pulsatile release implants and microparticles (Ganiyu Jimoh et al. 1995; Makino et al. 2000; Meinel et al. 2001). The pulsatile release from PLGA microparticles is frequently referred to as a release with an initial burst and a rapid release separated by time intervals of no drug release (Medlicott and Tucker 1999). Pulsatile release was obtained due to PLGAs properties and degradation (Makino et al. 2000; Meinel et al. 2001). Although the burst release in this case is favorable, the quantity of the burst probably cannot be controlled (Huang and Brazel 2001). It is better to achieve pulsatile release without the initial burst and where the lag time can be predicted and controlled.

Direct compression is a practical and less stressful method for preparing PLGA implants in comparison to other methods such as injection molding and hot-melt extrusion. Neither solvents nor heat are usually applied (Jivraj et al. 2000). Although direct compression is a risk-free method in relation to solvent toxicity and drug stability, the preparation of PLGA implants by this method usually results in implants with high porosity and rapid drug release (Negrín et al. 2004; Onishi et al. 2005). Additional methods to suppress or prolong the drug release from implants prepared by direct compression are necessary (Huang and Brazel 2001; Qian et al. 2001).

The objectives of this study were to achieve a pulsatile drug release profile without an initial burst from PLGA implants prepared by direct compression and to investigate parameters influencing drug release from PLGA implants. The selection of the material to incorporate into PLGA implants and the development and investigation of safety and biocompatibility were primarily concerns due to the parenteral route administration. A better understanding of mechanisms to achieve pulsatile release from PLGA implants helps for a successful formulation of parenteral pulsatile release. Manufacturing processes with easy scale-up, such as coating, were used in this study.

3.1.2. Results and discussion

Theophylline releases from PLGA compressed implants showed triphasic drug release profiles (Fig. 3.1). The initial release was followed by a slow release phase (lag time), and subsequently a rapid drug release due to PLGA degradation was (Bhardwaj and Blanchard 1997; Wang et al. 2002; Desai et al. 2008). The drug release profiles, particularly the initial release, depended upon drug loading (Fig. 3.1). Since the drug particles were embedded into the PLGA implant in the form of solids, the increase in the initial release as theophylline loading increased was attributed to more interconnection between the drug particles. Before the pores created by the dissolved and released drug particles were closed during the lag phase (day 2 - day 10) (Wang et al. 2002), a higher drug loading led to a higher matrix porosity, resulting in a larger initial burse release (Murty et al. 2004; Liu et al. 2006).

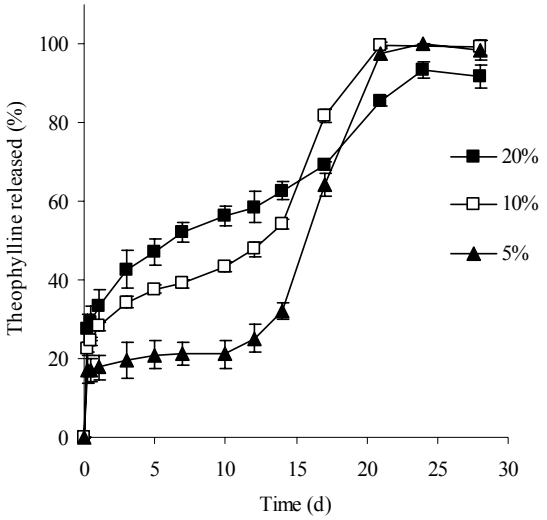


Fig. 3.1. Effect of drug loading (% w/w) on theophylline release from PLGA 503H implants

PLGA coating of PLGA compressed implants, and reduction of implant porosity by dipping the implants into methylene chloride, decreased the drug release, particularly the burst release (Fig. 3.2). The decrease in drug release (both theophylline and dexamethasone salt) was explained by a reduction of initial burst. Drug particles at the outer part of an implant or microparticles could release rapidly before the pores inside the PLGA implants have been closed by the polymer swelling. The rapid and large amount of release at this early phase has been known as an initial release (Huang and Brazel 2001; Wang et al. 2002). The coating

could prevent the initial burst release by the additional layer of polymer. The coating layer functioned as a barrier to the release of the drug particles at the outer section of the implant resulting in a decrease in the initial release. The solvent dipping caused the pores at the outside of implants to close due to the dissolution of the polymer, thus causing a decrease in the drug release by a similar mechanism as the coating effect. A fast release from 10% w/w dexamethasone salt (the water soluble drug) loaded PLGA implants was found. Without coating, dexamethasone salt was released within 6 hours (Fig. 3.2a). Coating could extend dexamethasone release from PLGA implants, and the drug release continued until 7 days. However the drug releases of implants coated with different concentrations of coating solution were similar (Fig 3.2). The influence of the coating was more pronounced for theophylline loaded implants (Fig. 3.2a) in comparison to dexamethasone salt loaded implants (solubility 433.2 ± 13.7 mg/ml in phosphate buffer pH 7.4, at 37°C) because of the lower water solubility of theophylline (13.67 ± 0.43 mg/ml in phosphate buffer pH 7.4, at 37°C) (Özgüney et al. 2009). A pulsatile release without an initial burst release was achieved from the theophylline loaded PLGA implants (Fig. 3.2a). After a lag time (day 0 - day 9), theophylline was released rapidly due to PLGA degradation (Fig. 3.2a). A greater amount of water uptake by the generated acid degradation products in combination with a lower remaining mass after several days (Fig. 3.3b) resulted in a rapid theophylline release after the lag time. For PLGA implants coated by a higher concentration of the coating solution, a higher weight gain of the coated implants was found due to the thicker coating layer (Table 3.1). However no influence of the concentration of the coating solution (50 and 200 mg/ml) on the lag time has been observed. The slightly faster drug release after the lag time was only found in comparison with the implants dipped into methylene chloride (Fig 3.2a). More accumulation of acid degradation products from PLGA as a result of higher weight gain (Table 3.1) and a thicker coating layer caused autocatalysis and a faster PLGA degradation. This resulted in slightly faster theophylline release after the lag time.

More processes to create a denser PLGA matrix are needed to slow the release of the water-soluble drug. Dexamethasone salt released rapidly from PLGA implants prepared by compression (Fig. 3.4). The drug releases was complete (more than 90%) within 1 day, 3 days and 7 days for only compression, compression with curing, and compression with coating, respectively. The combination of curing and coating could slow dexamethasone salt release. The release was prolonged until 2 weeks and exhibited a continuous release profile.

Curing at a temperature above the glass transition temperature of PLGA (PLGA 503H, 44.4 °C) generated a less porous matrix. For dip coating, the decrease in dexamethasone salt release was attributed to the coating layer and the fusion of PLGA caused by the presence of methylene chloride as the solvent of the coating solution. The synergistic effect of curing and coating was necessary to control dexamethasone release because of its high water solubility (433.2 ± 13.7 mg/ml in phosphate buffer pH 7.4 at room temperature).

Table 3.1. Weight gain and lag times of PLGA implants

Core	Coating material	Concentration of coating solution (mg/ml)	Additive	Weight gain (%w/w)	Lag time (d)
PLGA 503H	-	-	-	-	7.6[a]
	PLGA 503H	50	-	1.75 ± 1.12	8.2
		200	-	7.24 ± 1.75	7.8
	PLGA 502H	200	-	5.99 ± 0.69	5.5
	PLA 202H		-	7.20 ± 1.20	11.4
	PLGA 502H	200	5% $Mg(OH)_2$[b]	8.50 ± 1.01	-
	PLA 202H		5% $Mg(OH)_2$[b]	6.22 ± 0.47	-
PLGA 502H	PLGA 503H	200	-	5.11 ± 0.85	2.4
	Tripalmitin	-	-	4.18 ± 1.59	4.3
			3% NaCl[b]	4.66 ± 2.61	4.4
			3% $Mg(OH)_2$[b]	5.89 ± 1.98	7.9

[a] Implants dipped into methylene chloride

[b] % w/w based on core implants

Lag times of the pulsatile release from theophylline loaded PLGA implants could be modified by changes in the molecular weight of PLGA for the implant core and the coating solution (Fig. 3.5 and Table 3.1). For PLGA implants coated by the same polymer solution the lag time could be extended by use of a higher PLGA molecular weight as the implant core (Fig. 3.5a and Table 3.1). The lag time was prolonged for 5 days when PLGA 502H was replaced in the cores with PLGA 503H. After the lag times, the release profiles were in parallel (Fig. 3.5a). This finding was attributed to changes in PLGA degradation. Higher PLGA molecular weight has a larger inherent viscosity of PLGA and degraded slower

(Omelczuk and McGinity 1992; Pham 2004). The rapid release phase due to PLGA degradation was delayed as a result of the longer lag time. The replacement of PLGA 502H by PLGA 503H for the coating solution also resulted in longer lag time (Table 3.1). The lower inherent viscosity of PLGA 502H, and thus lower weight gain, was used to explain this result. Theophylline could diffuse more easily through the thinner coating layer, which could be detected by the low weight gain of the coated implants. On the other hand, the lag time of theophylline release was prolonged when using a PLA coating solution as the coating solution (Fig. 3.5b and Table 3.1). A lag time of 11 days without an initial burst release was observed. With a similar weight gain as the PLGA 503H coating, the lag time of theophylline was longer due to its higher hydrophobicity and the longer degradation time of PLA (Ramchandani et al. 1997; Lu et al. 1999; Wu and Wang 2001; Pham 2004).

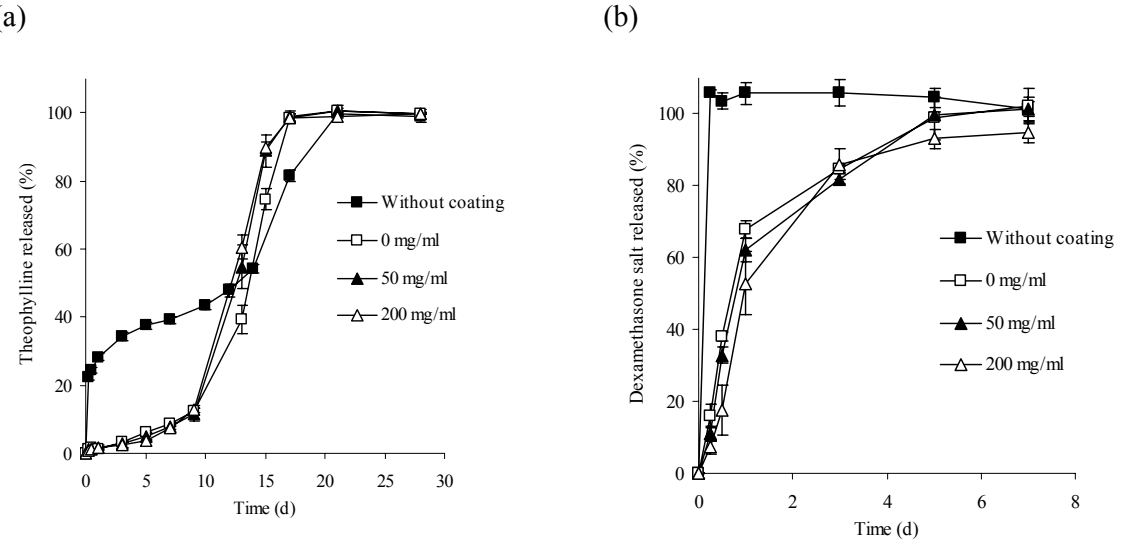


Fig. 3.2. Effect of dip coating and change in coating solution concentration on drug release (a) theophylline and (b) dexamethasone salt from PLGA coated implants containing 10% w/w drug loading; core polymer, PLGA 503H; coating solution, PLGA 503H in methylene chloride

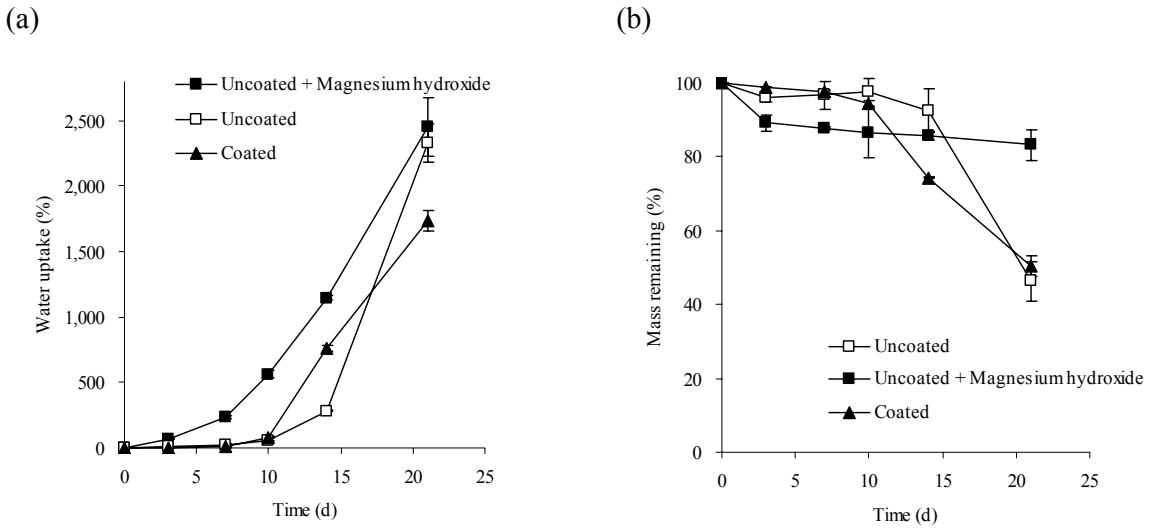


Fig. 3.3. PLGA 503H implants containing 10% w/w theophylline (a) water uptake and (b) mass remaining

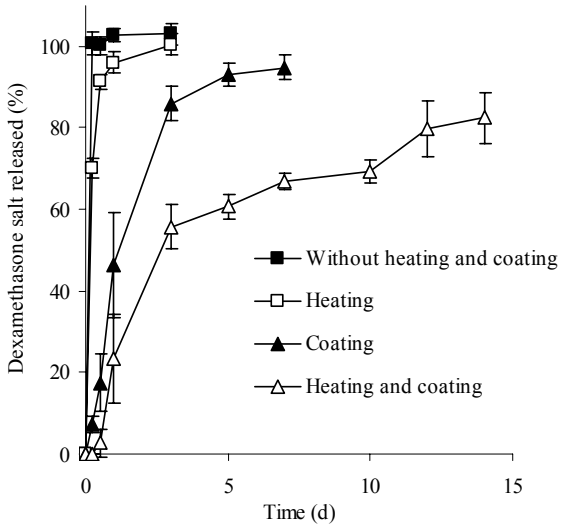


Fig. 3.4. Dexamethasone salt release from PLGA 503H implants containing 10% w/w drug loading; coating solution, 200 mg/ ml PLGA 503H in methylene chloride; heating at 50°C 15 min

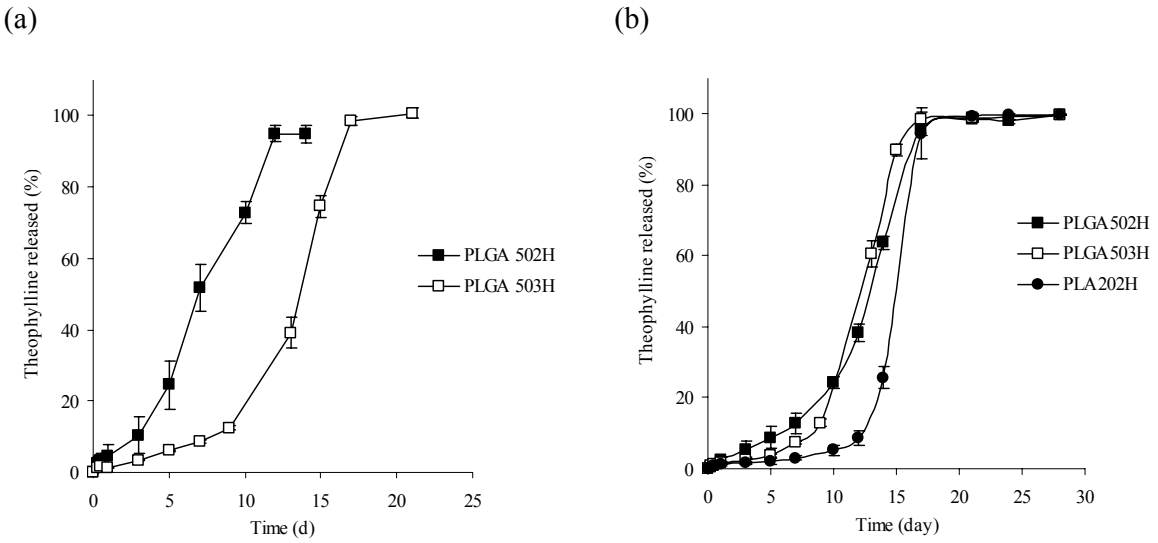


Fig. 3.5. Effect of polymer (a) type of core and (b) coating polymer on theophylline release from PLGA coated implants containing 10% w/w drug loading; (a) coating solution, 200 mg/ml PLGA 503H in methylene chloride and (b) implant core, PLGA 503H

The addition of 5% w/w magnesium hydroxide ($Mg(OH)_2$) (based on the polymer) into PLGA 503H cores modified the theophylline release (Fig. 3.6). A continuous release of theophylline was achieved regardless of the coating solution type (PLGA or PLA solution) (Fig. 3.6). This can be explained by the higher water uptake of the PLGA implant containing 5% w/w $Mg(OH)_2$ (Fig. 3.3a) and the rapid theophylline release from the PLGA implant containing 5% w/w $Mg(OH)_2$ without coating (> 90% release within 3 days). The addition of $Mg(OH)_2$ raised the microclimate pH of PLGA implants (saturated $Mg(OH)_2$, pH = 9.90), and thus the carboxylic end groups of both lactic acid and glycolic acid were ionized. The ionization of the polymer end groups and the osmotic gradient due to the incorporation of $Mg(OH)_2$ in the implants led to higher water uptake. Moreover, theophylline solubility was increased as the pH in the microclimate increased resulting in a greater amount of drug release during the lag time phase (Serajuddin and Jarowski 1985). In addition, the complete (100%) release of theophylline was extended by the incorporation of 5% w/w $Mg(OH)_2$ into the core of PLGA coated implants (Fig. 3.6). This finding was explained by the higher mass remaining as a result of slower PLGA degradation (Fig. 3.3b). The presence of 5% w/w $Mg(OH)_2$ in the core resulted in the inhibition of autocatalytic degradation, the neutralization of the acidic microclimate, and an increase in the porosity. Slow PLGA degradation lead to the extension of the theophylline release (Zhang et al. 1997; Zhu and Schwendeman 2000).

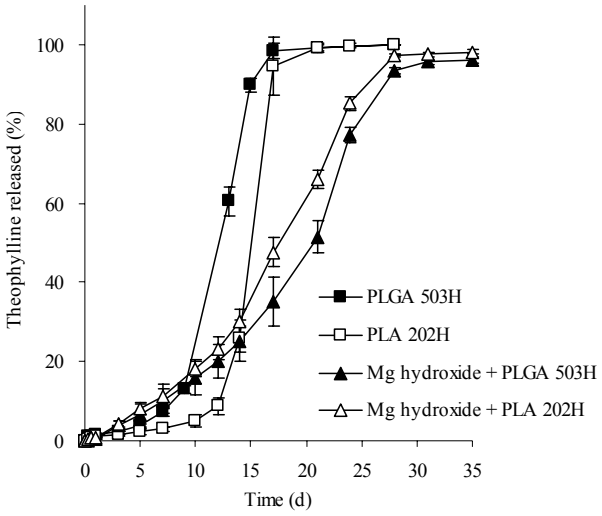


Fig. 3.6. Effect of adding 5% w/w magnesium hydroxide (based on the core) into the core of PLGA coated implants on theophylline releases containing 10% w/w drug loading; core polymer, PLGA 503H; coating solution, 200 mg/ml PLGA 503H and PLA 202H in methylene chloride

Coating PLGA implants loaded with 10% w/w theophylline with tripalmitin demonstrated pulsatile release pattern without an initial burst release (Fig. 3.7a). Rapid theophylline release within 2 days after a lag time of 5 days was observed. The pulsatile release pattern from tripalmitin coated PLGA implant was obtained due to the rupture of the tripalmitin layer (Fig. 3.8). After the PLGA implant took up water and swelled, the thinner coating layer at the edge ruptured behavior (Béchard et al. 1995). Salts (NaCl and $Mg(OH)_2$) were added into the PLGA cores in order to increase the water uptake. Since it was hypothesized that the pulsatile release of theophylline was due to the rupture of the tripalmitin layer caused by the water uptake, a change in lag time was predicted when salt was added. Surprisingly, the lag time of theophylline release was extended by the addition of 3% w/w $Mg(OH)_2$ (based on the polymer) (Fig 3.7a), where a greater amount of water uptake (Fig. 3.7b) and more swelling of the implants was visually observed in comparison to the additive-free PLGA implants, and the core implants containing 3% w/w sodium chloride (NaCl) (Kang and Schwendeman 2002). Through the addition of $Mg(OH)_2$ the lag time was prolonged by more than 2 days. The neutralization effect of $Mg(OH)_2$ on the acidic microclimate of the PLGA implants was the dominant mecahnism. Subsequently, theophylline release was controlled by the PLGA

polymer, which degraded more slowly due to the effect of $Mg(OH)_2$ (Zhang et al. 1997). A change in theophylline release was not obtained when NaCl was incorporated into the core. Similar pulsatile release profiles were explained by the comparable water uptake, and the fact that NaCl does not influence the PLGA degradation (Fig. 3.7b).

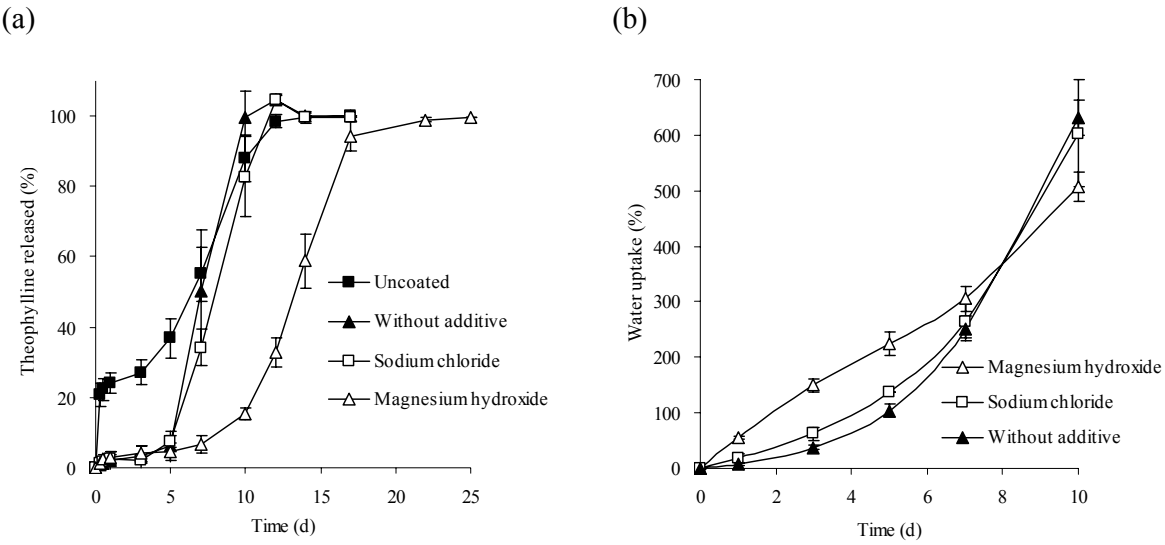


Fig. 3.7. Theophylline releases from coated PLGA 502H implants (a) drug release and (b) water uptake of uncoated implants; core polymer, PLGA 502H; coating material, tripalmitin

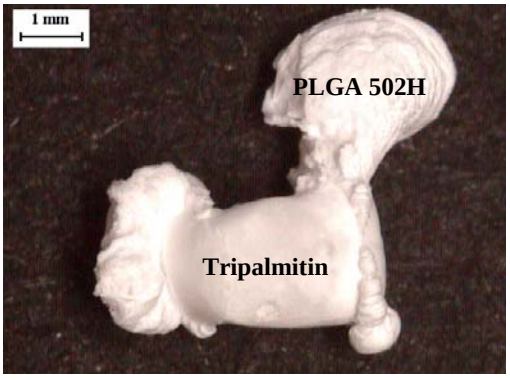


Fig. 3.8. Rupturing behavior of PLGA 502H coated implant was monitored at day 7; coating layer, tripalmitin

In this section, the different coating materials of PLGA implants are compared and discussed regarding the drug release and the release mechanism. Both coating materials could suppress the initial release of theophylline from PLGA implants (Fig. 3.9). The coating acted as a

drug-free layer regardless of the type of material. The presence of the coating layer slowed the drug diffusion, resulting in a smaller initial release, or no initial release, from PLGA implants containing 10% w/w theophylline. Tripalmitin coated implants showed a longer lag time than PLGA 503H coated implants (Table 3.1). During the period of the lag time a lower release of theophylline from tripalmitin coated implants was observed on day 1 – day 5 (Fig. 3.9). These results were explained by the theophylline diffusivity. Theophylline has a smaller diffusivity in tripalmitin (1.42×10^{-9} cm^2/s) than in PLGA 503H (2.21×10^{-8} cm^2/s) which led to less theophylline release, and thus a longer lag time. The different pulsatile mechanisms demonstrated the different rates of theophylline release after the lag time (Fig. 3.9). The tripalmitin film is more brittle than the PLGA 503H film (by visual observation) thus creating the rupture behavior shown in Fig. 3.8, which results in a rapid theophylline release. In contrast to the tripalmitin coating, pulsatile release from the PLGA coating was obtained by the acceleration of PLGA degradation due to the presence of the coating layer, but the coating layer remained intact. The drug released slowly after the lag time.

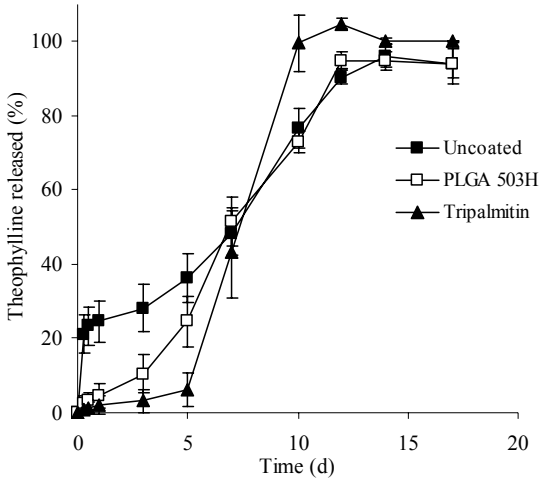


Fig. 3.9. Comparison of different coating materials on theophylline release from PLGA 502H implants

3.1.3. Conclusion

The release pattern of PLGA implants depended on the drug solubility. For highly water-soluble drugs such as dexamethasone salt, a continuous release profile was achieved by the

combination of curing and coating after compression to form the implants. A pulsatile release was obtained from theophylline loaded PLGA implants, a model for slightly water-soluble drugs. The initial burst release from theophylline implants was suppressed by coating and solvent dipping due to the presence of a release barrier and sealing of the pores on the surface of the implants, respectively. The lag time of the pulsatile release could be controlled by changes in the implant cores and coating materials. The replacement of the implant core by PLGA of a higher inherent viscosity led to a longer lag time as a result of a longer degradation time. The lag times could also be prolonged by a change in coating material from PLGA 502H to PLGA 503H. Using tripalmitin as a coating material resulted in a longer lag time compared to using PLGA as a coating material, and the mechanism of pulsatile release was changed from degradation of the polymer core to the rupture of tripalmitin. PLA as a coating material caused a prolonged lag time in comparison with PLGA due to its longer degradation time. The addition of $Mg(OH)_2$ into the core provided a continuous and sustained theophylline release regardless of the type of polymer coating.

3.2. Pulsatile release pattern from PLGA hot-melt extruded implants: Influence of processing parameters, drug properties and in vivo simulation

3.2.1. Introduction

Pulsatile release is defined as a zero drug-release period (a lag time) followed by a rapid and complete release within a short period of time (Krögel and Bodmeier 1997; Kikuchi and Okano 2002). For parenteral drug delivery systems, a pulsatile release pattern is useful for some drugs, such as parathyroid and follicle stimulating hormone, in order to avoid adverse effects and achieve the desired therapeutic effects (Ganiyu Jimoh et al. 1995; Liu et al. 2007). Due to the route of administration of parenteral pulsatile release systems, the safety and biocompatibility of the drug carrier are significant concerns. One suitable polymer for this application is PLGA. It has been widely used for parenteral drug delivery systems and is reported to allow the preparation of self-regulated pulsatile release systems. The pulsatile release is achieved owing to the rapid drug release after the critical point of the polymer degradation erosion (Liu et al. 2007).

Several factors have been shown to have an affect on drug release profiles from PLGA implants, particularly a pulsatile release pattern. Pulsatile release can be achieved due to the degradation-dependent drug release of the PLGA implant (Fitzgerald and Corrigan 1996; Bhardwaj and Blanchard 1997). Every factor influencing PLGA degradation has an effect on drug release. Degradation is dependent on PLGA molecular weight (Bhardwaj and Blanchard 1997; Tracy et al. 1999), lactide:glycolide monomer ratios (Ramchandani et al. 1997; Lu et al. 1999; Eliaz and Kost 2000), size of drug delivery system (Vert et al. 1994; Lu et al. 1999; Burkersroda et al. 2002; Klose et al. 2008), etc. Faster PLGA degradation leads to a faster drug release or a shorter duration of action (Kunou et al. 1995; Ramchandani et al. 1997). Moreover, differences in preparation methods, such as the adjustment of processing parameters, drug loading and drug properties, has an impact on the drug release (Kunou et al. 1995; Fitzgerald and Corrigan 1996; Bhardwaj and Blanchard 1997; Miyajima et al. 1998; Eliaz and Kost 2000; Klose et al. 2008). An increase in drug loading results in a larger or faster drug release. The incorporation of an acid drug or other drug properties into an implant leads to modification of the drug release profile caused by some interaction, drug diffusivity,

or changes in PLGA degradation. A better understanding of the influence of the polymer, drug properties and processing parameters on the release profiles from PLGA implants can enhance the formulation of an implant drug delivery system, and create a desired, controllable and predictable drug release profile.

The Fédération Internationale Pharmaceutique/ American Association of Pharmaceutical Scientists (FIP/ AAPS) recommend a flow-through cell apparatus for studying drug release of implants (Stiewert et al. 2003; Iyer et al. 2006). A main disadvantage of this method is the direct exposure to a release medium (frequently a buffer solution), whereas in vivo condition an implant is placed subcutaneously or into a specific site of action surrounded by body tissues (Iyer et al. 2006; Klose et al. 2008). From the literature, the most commonly used method to determine a drug release was an agitated or a shaking method in a closed container and a controlled environment, due to ease of manipulation and the practicality of these types of methods (Bhardwaj and Blanchard 1997; Dorta et al. 2002; Eperon et al. 2008). Due to the requirement of a simple but more realistic in vivo condition, it is necessary to modify in vitro drug release studies for implant drug delivery. When subcutaneous implantation is used, the implant is in contact with adipose and connective tissue in the subcutaneous layer. Therefore a more lipophilic medium should be applied in studies of drug release.

The objectives of the current study were to study the influences of different drug properties on drug release, thermal and physical properties, and to modify lag-times of pulsatile drug release from PLGA implants. Small molecular weight drugs with different water solubilities and melting points (T_m) were used as model drugs. In addition, a common release medium (phosphate buffer pH 7.4) for studies of implant drug release was replaced by a parenteral lipid emulsion in order to mimic subcutaneous tissue conditions (Bhardwaj and Blanchard 1997; Dorta et al. 2002; Eperon et al. 2008).

3.2.2. Results and discussion

Several factors should be considered to achieve a desired pulsatile release with a preferred lag time from PLGA based implants. The pulsatile release pattern can be controlled and modified by understanding the influences of each parameter on the drug release from PLGA. Drug properties, drug loading and processing parameters cause various drug release profiles due to

the properties of PLGA. Optimal values of these factors should result in an appropriate pulsatile release profile. Since implants are exposed directly to subcutaneous tissues after administration (Iyer et al. 2006), a more realistic in vitro release method to simulate an in vivo condition should be considered. For subcutaneous implantation, a normal release medium (phosphate buffer pH 7.4) was replaced by a more lipophilic solution in an attempt to mimic subcutaneous administration of implants. Lipofundin^{TM} was chosen as the medium due to composition of the subcutaneous skin layer that consists of adipose tissues (Barry 1983; Timby and Smith 2006).

The inherent viscosity of PLGA, extrusion temperature, drug loading and drug properties had an impact on the melt viscosity during extrusion, as represented by maximum torque (Table 3.2). The preparation of implants by PLGA with a higher inherent viscosity (PLGA 502H, 0.16 – 0.24 dl/g and PLGA 503H, 0.32 – 0.44 dl/g) resulted in higher maximum torques. An increase in extrusion temperatures from 80 °C to 100 °C reduced the maximum torques. An increase in the amount of solid particles in the mixtures as a result of higher drug loading of dexamethasone salt caused elevated maximum torques. The effect of incorporating different drug at similar loading (10% w/w) on maximum torques was classified into three groups (Table 3.2). The incorporation of tramadol HCl into PLGA implants increased the maximum torques compared to no drug loading, whereas the presence of diazepam and dexamethasone had less influence on the maximum torques. Another effect was a decrease in the maximum torques by the addition of ibuprofen. Ibuprofen not only decreased the maximum torque but the T_g of PLGA was also suppressed by the addition of ibuprofen (Table 3.3). For both PLGA 502H and PLGA 503H, the effect of ibuprofen on T_g was similar. Moreover, the crystalline peak of ibuprofen virtually disappeared for the PLGA implant containing 10% w/w ibuprofen due to the low drug melting point (Fig. 3.10 and Table 3.4), which is close to the extrusion temperature used. Ibuprofen was partially dissolved in the PLGA and acted as a plasticizer for the PLGA. From the literature, ibuprofen interacts with ethyl cellulose and ammonio methacrylate copolymer (Type B) (Eudragit® RS) by forming a hydrogen bond (Wu and McGinity 2001; Brabander et al. 2002). In the case of PLGA and ibuprofen, the hydrogen bond probably occurs through the carboxylic acid group of ibuprofen and the ester groups of the polymer, similar to that noted previously with other polymers. In contrast with ibuprofen, there was little or no influence of tramadol HCl, dexamethasone salt, or diazepam on the T_g (Table 3.3).

Table 3.2. Maximum torques during hot-melt extrusion at 80°C; screw rotation speed, 20 rpm

Polymer	Drug	Extrusion temperature (°C)	Drug loading (%)	Maximum Torque (Nm)
PLGA503H	-	80	-	0.84
	Tramadol HCl		10	1.26
	Ibuprofen			0.30
	Diazepam			0.65
	Dexamethasone salt			0.52
			20	0.63
		100	10	0.17
PLGA502H	-	80	-	0.21
	Tramadol HCl		10	0.39
	Ibuprofen			0.10
	Diazepam			0.30
	Dexamethasone salt			0.25
			20	0.30
		100	10	0.10

Table 3.3. T_g, initial release and lag time of PLGA implants

Drug	10% w/w drug loading						20% w/w drug loading	
	T_g (°C)		Initial release (%w/w)		Lag time (d)		Initial release (%w/w)	
	PLGA 502H	PLGA 503H	PLGA 502H	PLGA 503H	PLGA 502H	PLGA 503H	PLGA 502H	PLGA 503H
-	40.58	45.90	-	-	-	-	-	-
Tramadol HCl	40.41	43.79	10.28 ± 0.71	5.05 ± 0.49	1.0	7.4	9.83 ± 2.44	8.30 ± 1.06
Dexamethasone salt	39.54	42.95	7.38 ± 1.22	2.78 ± 0.21	4.2	9.8	12.51 ± 1.33	12.54 ± 0.18
Ibuprofen	28.09	32.74	3.31 ± 0.47	2.63 ± 1.32	1.4	2.5	-	-
Diazepam	42.90	45.06	0.48 ± 0.43	0.48 ± 0.46	6.9	12.8	0.87 ± 0.61	1.57 ± 0.32

The drug releases from PLGA implants prepared by hot-melt extrusion displayed a pulsatile release pattern (Fig. 3.11). The incorporation of 10% w/w of different model drugs with various drug physical properties (Table 3.4) into PLGA implants resulted in various lag-times and initial releases. The comparable triphasic releases from tramadol HCl, dexamethasone salt and ibuprofen loading implants were found, but the equivalent release of diazepam was not found. The triphasic release consisted of a small initial drug release, followed by a slow

release phase due to drug diffusion, followed by a rapid release as a result of the PLGA erosion (Kunou et al. 1995; Bhardwaj and Blanchard 1997). Less than 1% cumulative drug release within the first day resulted in a biphasic release pattern from diazepam loaded implants. The phase of no drug release with the second phase of the rapid release is illustrated. Implants containing drugs with higher drug solubilities in water (Table 3.4) showed larger initial drug release (Fig 3.11 and Table 3.3). The incorporation of drugs with high solubility led to shorter lag times (Fig 3.11 and Table 3.3). The shorter lag times of ibuprofen could be explained by its plasticizing effect on PLGA, higher water uptake and faster mass loss in comparison to the implants containing the other drugs (Fig. 3.12). Although the solubility of tramadol HCl was higher than dexamethasone salt, the basic property of tramadol HCl led to a slower release than dexamethasone salt (an acidic drug) at the tertiary release phase (the rapid release phase after the lag time) (Fig. 3.12). The basic drug (having a positive charge) could form an ionic interaction with the negative charge of the deprotonated carboxylic end group of PLGA resulting in more prolonged PLGA degradation (Fig. 3.12b) and slower drug release (Fig. 3.11) (Miyajima et al. 1998; Klose et al. 2008). In addition, the PLGA inherent viscosity influenced the initial drug release and lag time (Table 3.3). A higher inherent viscosity resulted in longer lag times and less initial drug release (Bhardwaj and Blanchard 1997) because of the higher molecular weight of PLGA, and thus slower PLGA degradation (Tracy et al. 1999; Alexis 2005).

Table 3.4. Melting points and solubility of model drugs in phosphate buffer pH 7.4

Drugs	Solubility (mg/ml)	Melting point (°C)
Tramadol HCl	793.5 ± 97.8 [a]	171 – 173 [1]
Dexamethasone salt	433.2 ± 13.7 [a]	224 – 229
Ibuprofen	7.0 ± 0.1 [b]	78 – 80 [2]
Diazepam	0.2 ± 0.02 [b,c]	131 – 136

[a] = at room temperature; [b] = at 37°C; [c] = with the addition of 0.1% w/v SDS

[1] (Buschmann et al. 1998)

[2] (Kidokoro et al. 2001)

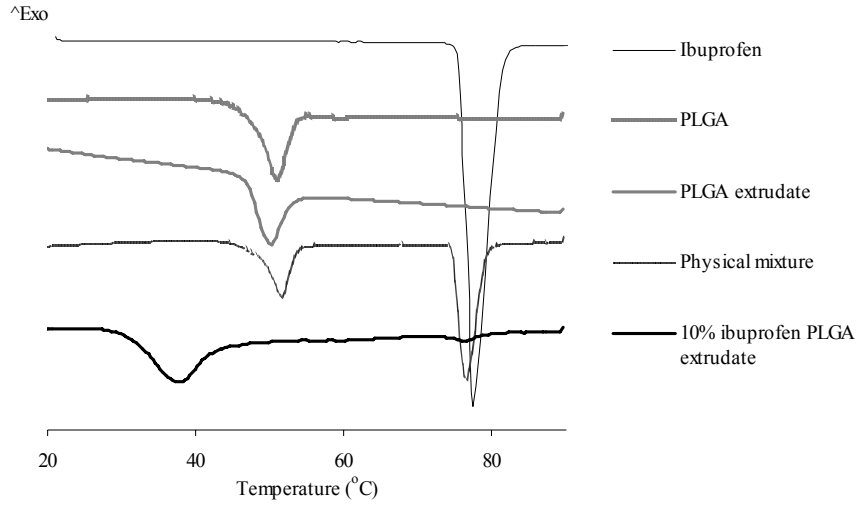


Fig 3.10. DSC thermogram (first run) of PLGA 503H, ibuprofen, physical mixture of 10% w/w ibuprofen and PLGA 503H, PLGA 503H extrudates and PLGA 503H extrudates containing 10% w/w ibuprofen

(a) (b)

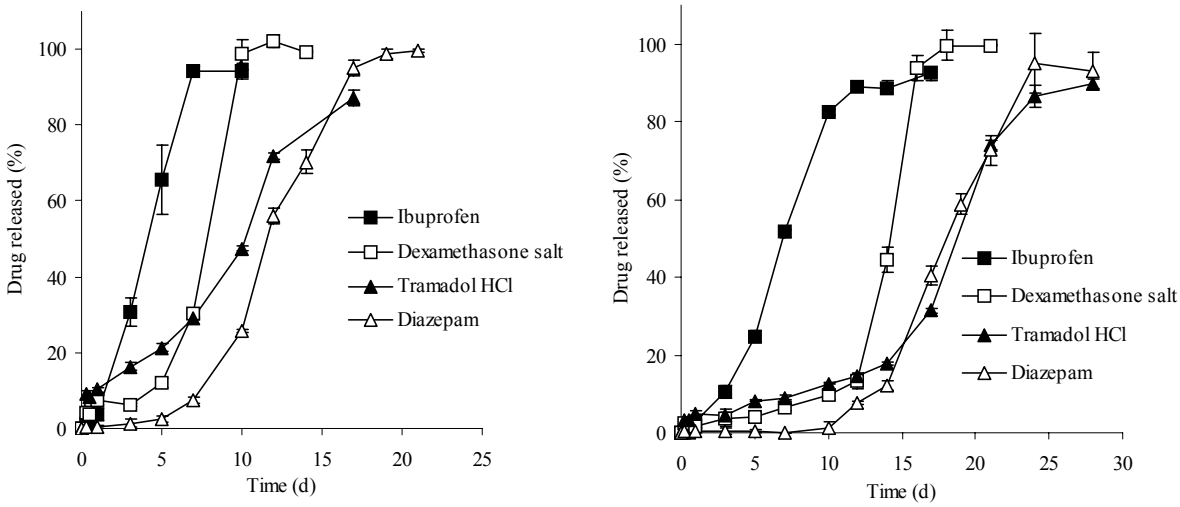


Fig. 3.11. Drug releases from PLGA implants containing 10% w/w drug loading (a) PLGA 502H and (b) PLGA 503H

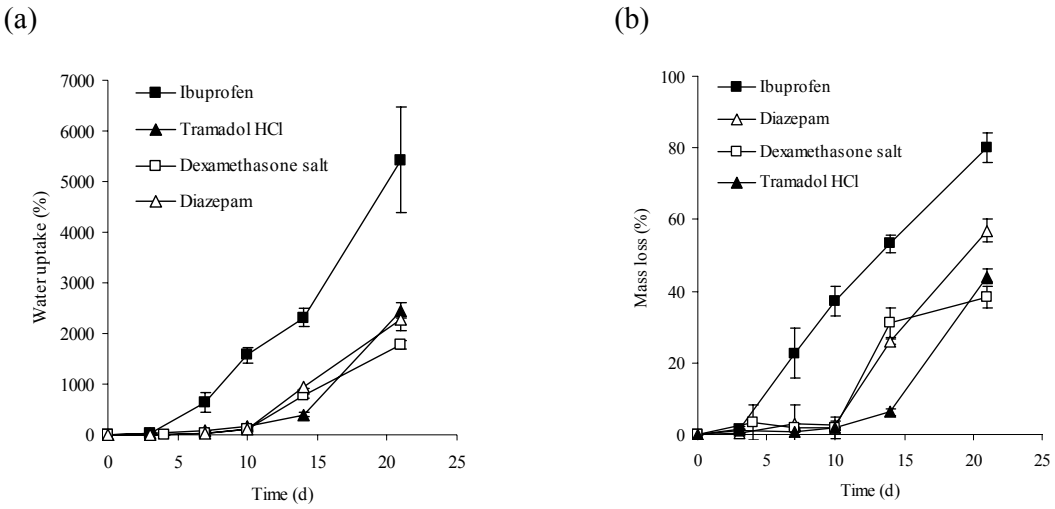


Fig. 3.12. Physical properties of PLGA 503H implants containing 10% w/w drug loading (a) water uptake and (b) mass loss

The increase in drug loading from 10% to 20% w/w led to a larger initial drug release (Table 3.3 and Fig. 3.13). In particular, this finding was noticeable for the implants containing the highly water-soluble drugs, tramadol HCl and dexamethasone salt, due to the small initial release from the implants containing the low water-soluble drug (diazepam). The lag times of the drug releases from 10% and 20% w/w drug loading were similar. Since the drug release from the PLGA implants was degradation-dependent, the degradation time of PLGA polymer plays a more important role on the lag time of the drug release than the drug loading (Fig. 3.13). The increase in drug loading did not affect tramadol HCl and dexamethasone salt releases at the rapid drug release phase, whereas the rapid release phase of diazepam was prolonged with increasing drug loading. The increase in drug release duration (from the end of the lag time until complete release) with the increase in drug loading was explained by the percolation-limited diffusion theory. The theory separates a drug loading into mobile drug molecules and immobilized drug molecules. The immobilized drug molecules can diffuse when the pore size increases by the hydrolytic degradation of PLGA (Tzafriri 2000; Iyer et al. 2007). In the case of a drug with low solubility, such as diazepam, the diffusion and dissolution of the immobilized drug were limited by its solubility. Therefore, the drug release duration during the rapid release phase was increased when the drug loading was increased from 10% to 20% w/w. By contrast, tramadol HCl and dexamethasone were freely released due to their high water solubility.

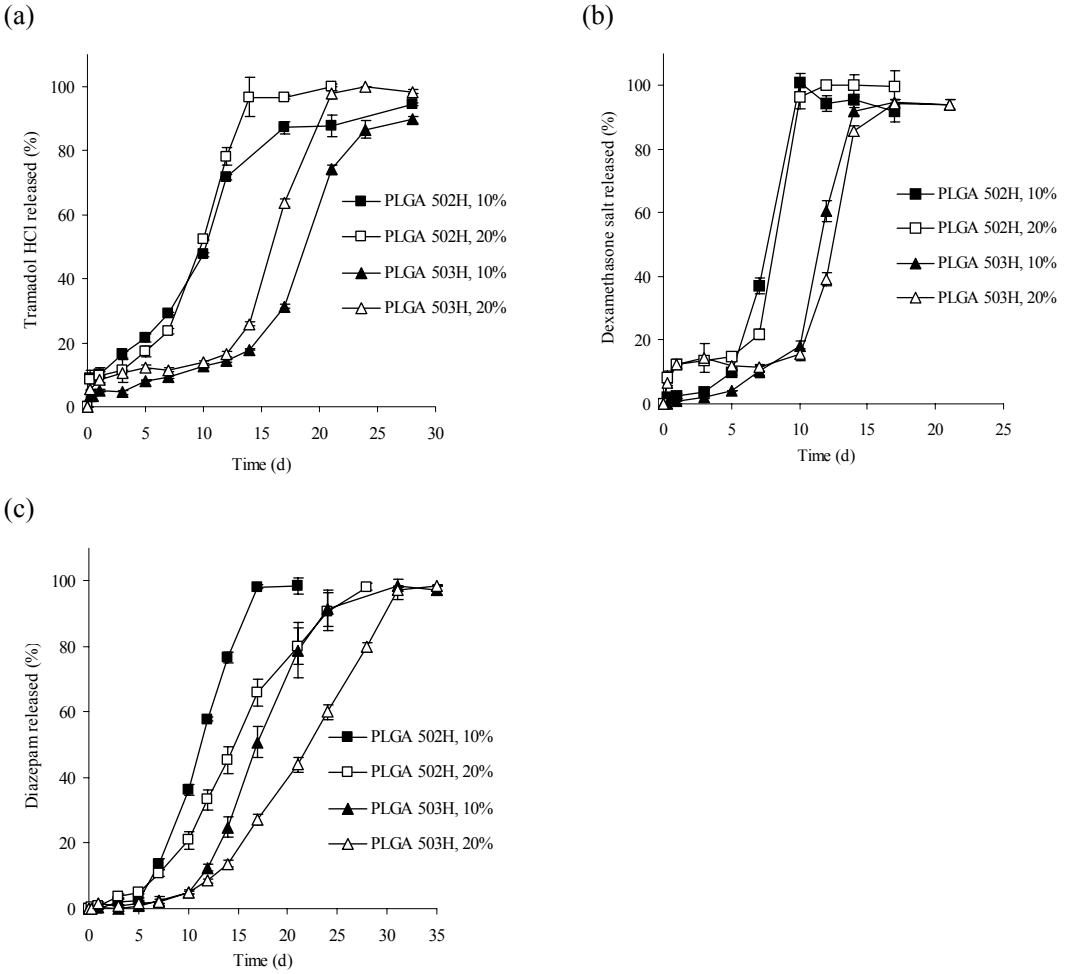


Fig. 3.13. Drug releases from PLGA implants containing 10% and 20% w/w drug loading (a) tramadol HCl (b) dexamethasone salt and (c) diazepam

Modification of processing parameters and coating had an effect on the lag time of pulsatile releases from PLGA implants (Fig. 3.14 and Table 3.5). An increase in extrusion temperature led to a shorter lag-time (Fig. 3.14a and Table 3.5) if the other parameters were unchanged. The lag times were shortened to approximately 1 day for the PLGA 502H implant and 3 days for the PLGA 503H implant when the extrusion temperature was increased from 80 °C to 100 °C. This result can be explained by the accelerated PLGA degradation. PLGA polymer undergoes bulk hydrolytic degradation and was degraded into acid byproducts. The acid degraded products could accelerate PLGA degradation, known as the autocatalytic effect (Lu et al. 1999). The denser matrix created by the increase in extrusion temperature (Yang et al. 2007) resulted in the more difficult diffusion of the acid degraded product. Faster PLGA degradation due to the higher accumulation of the degraded products occurred within the

implants prepared at the higher temperature, thus the observation of shorter lag time. By contrast, an increase in the diameter of the implant resulted in a longer lag time (Fig. 3.14b and Table 3.5). The lag times were extended due to the slower water penetration and drug diffusion. Water penetration into the implants was slower with the larger implant diameter upon exposure to the release medium. Since PLGA polymer degrades by hydrolysis, a slower PLGA degradation is expected for a larger implant diameter. Similar to the water penetration, the larger implant diameter led to a longer diffusion distance of the immobilized drug after the pore size was increased by the polymer degradation. In addition, coating PLGA implants by PLGA 503H solution resulted in a shorter lag time (Fig. 3.14c and Table 3.5). The accumulation of the PLGA degraded product that accelerated the polymer degradation can be used to explain this finding. The coating layer was a barrier for the diffusion of PLGA degradation product, and thus the degradation product was accumulated. Therefore a greater degree of autocatalysis and faster PLGA degradation occurred for PLGA implants with the presence of a coating layer.

Table 3.5. Effect of processing temperatures, die diameter and coating on lag-times of dexamethasone salt release profiles (Fig. 5)

PLGA 502H				PLGA 503H			
Temperature (°C)	Die diameter (mm)	Coated	Lag-times (d)	Temperature (°C)	Die diameter (mm)	Coated	Lag-times (d)
80	1	-	4.3	80	1	-	10.3
		+	3.2			+	6.1
100		-	3.1	100		-	7.5
	1.75		5.1		1.75		10.3

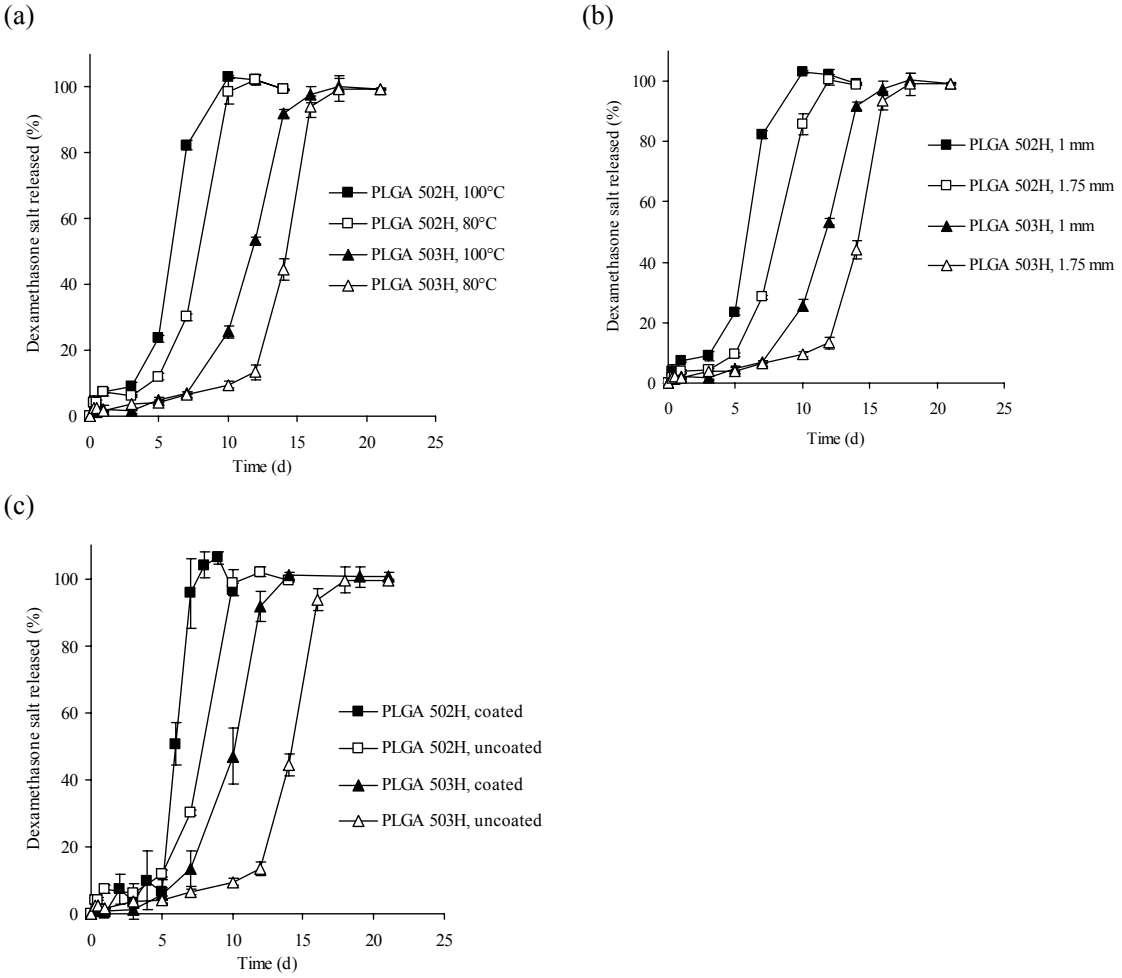


Fig. 3.14. Drug release form PLGA implants containing 10% w/w dexamethasone salt; effect of (a) extrusion temperatures (diameter, 1 mm), (b) diameter (extrusion temperature, 100°C) and (c) coating (diameter, 1 mm; extrusion temperature, 80°C; coating solution, 200 mg/ml PLGA 503H in methylene chloride)

The replacement of the commonly used release medium (phosphate buffer pH 7.4) by diluted Lipofundin^{TM} resulted in a higher release rate from 10% w/w diazepam PLGA 502H implants (Fig. 3.15a). Although the use of diluted Lipofundin^{TM} as a release medium had no influence on the mass loss of PLGA implants (Fig. 3.15c), the water uptake was decreased and the polymer swelling was suppressed (Fig. 3.15b and Fig. 3.16). The implants were deformed after 3 days of the immersion into the diluted Lipofundin^{TM}. The result was in agreement with in vivo study from the literature. The deformation of PLGA implants occurred in vivo instead of high water uptake and swelling. The swelling of PLGA in vivo was restricted by the

surrounding tissues and the mechanical stress from the movement (Kunou et al. 1995; Mäder et al. 1997). When using Lipofundin^{TM}, the implants became gel-like in appearance (Fig. 3.16). The T_g of the PLGA implants was decreased by the effect of the glycerin in Lipofundin^{TM} (Table 3.6). Diazepam diffused and released faster than when phosphate buffer was used, particularly during the phase that the drug releases mainly by diffusion, the phase of lag time (Eperon et al. 2008). To mimic the in vivo subcutaneous condition, using Lipofundin^{TM} was an alternative release medium for preliminary development of a more realistic in vitro drug release study of implants.

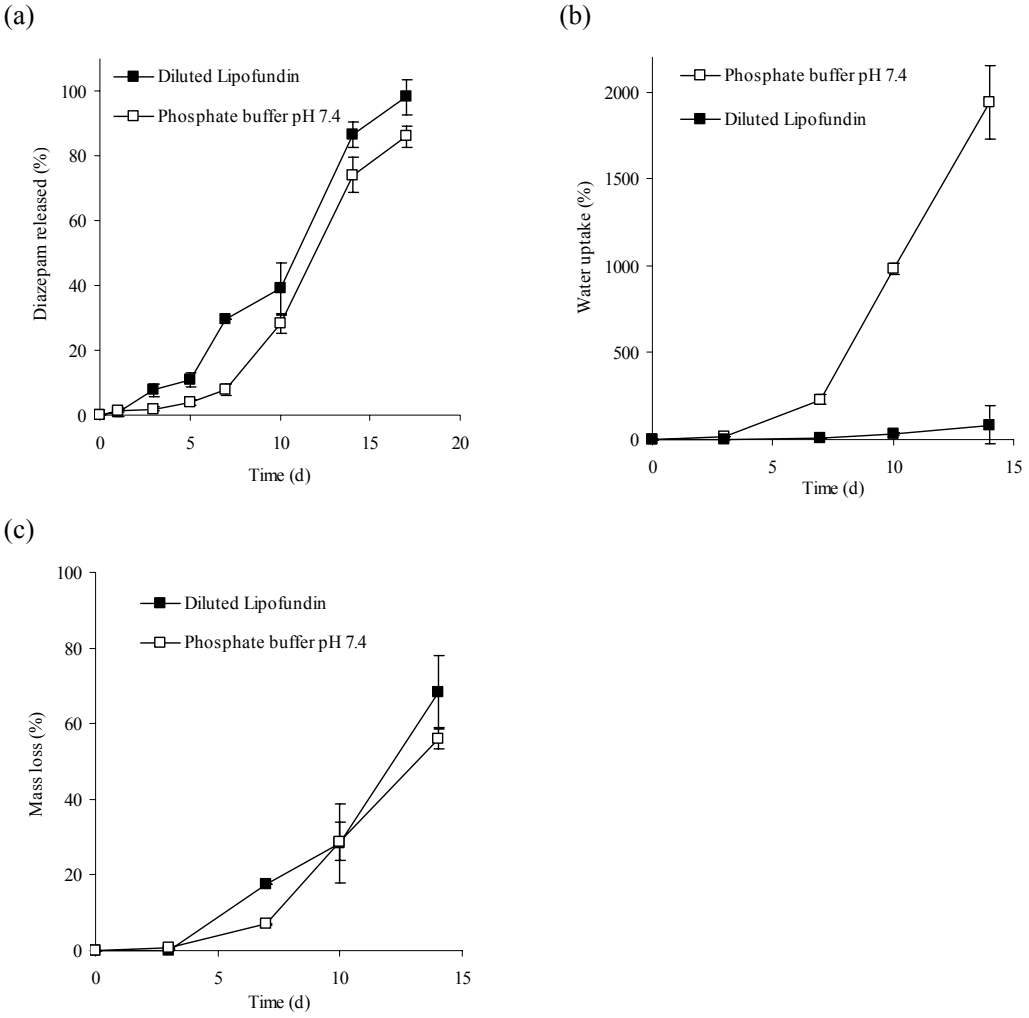


Fig. 3.15. Comparison between using diluted Lipofundin (1:4) and phosphate buffer pH 7.4 USP (a) release profiles (b) water uptake and (c) mass loss of PLGA 502H implants containing 10% w/w diazepam

(a) (b)

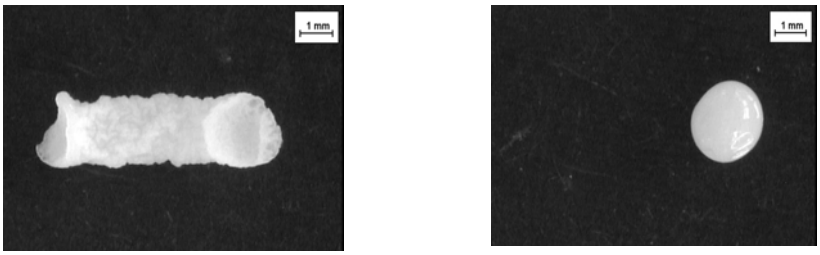


Fig. 3.16. Morphology of PLGA 502H implants containing 10% w/w diazepam in (a) phosphate buffer pH 7.4 and (b) diluted Lipofundin (1:4) at day 5

Table 3.6. Formulation of Lipofundin (MCT/ LCT 20%w/v) and the effect of each ingredient on T_g of PLGA 502H

Ingredient	Amount	T_g
Soybean oil (LCT)	100 g	40.28
Coconut oil (MCT)	100 g	39.62
Egg yolk lecithin	12 g	40.62
Glycerol	25 g	36.52
α-Tocopherol	0.2 g	-
Sodium oleate	0.3 g	-
Water for injection ad to	1000 ml	-

3.2.3. Conclusion

Maximum torques during hot-melt extrusion were dependent on the inherent viscosity of PLGA, extrusion temperature, drug loading and drug properties at a constant screw rotation speed. The incorporation of ibuprofen into PLGA reduced the maximum torque and T_g of PLGA by its plasticizing effect. A pulsatile drug release profile from PLGA hot-melt extruded implants was achieved, demonstrated by a lag time after an initial burst release, followed by a second burst or late rapid release phase. The plasticizing effect of ibuprofen on PLGA led to higher water uptake, faster mass loss, and thus the fastest drug release in comparison with the other model drugs. The initial burst release from PLGA implants prepared by hot-melt extrusion increased with an increase in drug loading, decrease in

inherent viscosity of PLGA and higher water solubility of the drug. The change in processing parameters, PLGA inherent viscosity, drug solubility and the presence of coating played an important role on the lag times of pulsatile release from PLGA implants. The factors generating the acceleration of PLGA degradation led to shorter lag-times, except the drug solubility. The second burst release phase was influenced by the drug solubility and acid-base properties. The release after the lag time was slowed with higher diazepam drug loading because of its low solubility. The release of a basic drug (tramadol HCl) was prolonged due to a possible ionic interaction. The replacement of phosphate buffer of pH 7.4 by Lipofundin to mimic in vivo subcutaneous tissue condition resulted in less water uptake, the deformation of the PLGA implant, and faster diazepam release during the diffusion phase due to the decrease in the T_g of PLGA, which is due to the presence of glycerol in the formulation.

3.3. Influence of additives on mechanism of drug release profiles from PLGA implants

3.3.1. Introduction

Poly(lactide-co-glycolide) (PLGA) is one of the biodegradable polymers used for parenteral drug delivery systems. Several techniques, such as hot-melt extrusion, compression and injection molding, can be used to form PLGA-based controlled release drug products. Among the preparation techniques, hot-melt extrusion is a successful commercial method for preparing PLGA-based drug delivery implants (Rothen-Weinhold et al. 1999). PLGA containing a drug or peptide is converted into a rod shape with a homogeneous drug distribution by applying heat. In general, hot-melt extrusion has to be proformed at a temperature above the glass transition temperature (T_g) of the polymer. The T_g of PLGA is approximately 40°C. Therefore, the processing temperature for PLGA hot-melt extrusion should be higher than 75°C (Mauriac and Marion 2006).

Plasticizers are incorporated into polymers in order to reduce the T_g and brittleness, adjust the mechanical properties, and improve the flexibility and workability of polymers (Wang et al. 1997; Brabander et al. 2002; Rahman and Brazel 2004). Plasticizers have been utilized in the process of hot-melt extrusion to improve the processibility of polymers (Repka et al. 1999; Zhu et al. 2006) and to lower the extrusion temperature (Wu and McGinity 2003; Zhu et al. 2006; Ghebremeskel et al. 2007; Verhoeven et al. 2008). The reduction of the processing temperature by the addition of a plasticizer increases the opportunity for heat labile drugs, such as peptides or proteins, to be fabricated in implants using hot-melt extrusion.

The choice of additives for parenteral drug delivery system is limited by toxicity and biocompatibility. Polyethylene glycol (PEG) is water-soluble and is accepted by the U.S. Food and Drug administration for parenteral use in humans (Zhu et al. 1990). It has been reported to be used as a plasticizer, solvent or solubilizing agent for pharmaceutical products (Schade et al. 1995; Rowe et al. 2003; Strickley 2004; Srinivasa et al. 2007). PEG has been extensively investigated as a plasticizer for polylactide hot-melt extrusion, especially poly(L-lactide) (PLA). The plasticizing effect of PEG on PLA extrudates has been demonstrated to reduce T_g, transform PLA from brittle to ductile behavior, and to improve the mechanical

properties of the polymer (Jacobsen and Fritz 1999; Baiardo et al. 2003; Pillin et al. 2006; Piorkowska et al. 2006). The presence of PEG in PLA allows ease of fabrication to be achieved. PEG has been added into PLGA films prepared by solvent casting for drug delivery. Previous studies showed only a reduction of T_g and change in the degradation of PLGA (Schade et al. 1995; Tan et al. 2004). The mechanical properties and physical stability of PEG in PLGA have not been described. In addition, PLGA-based implant drug delivery systems produced by hot-melt extrusion in the presence of PEG have not been studied.

Drug release profiles from most monolithic implant formulations based on PLGA or PLA have been reported as bi- or triphasic release patterns (Miyajima et al. 1998; Dorta et al. 2002; Viitanem et al. 2006; Naraharisetti et al. 2007). To overcome the weakness of drug release profiles from PLGA or PLA implants, triglycerides may be an alternative lipophilic additive. Since drug releases from triglyceride implants showed continuous profiles (Mohl and Winter 2004; Guse et al. 2006), bi- or triphasic releases from PLGA implants can probably be modified. In addition, triglyceride has been previously reported to be stable after hot-melt extrusion with low extrusion temperatures (Reitz and Kleinebudde 2007; Reitz and Kleinebudde 2007).

Triglycerides have been used, and are widely accepted, for preparation of parenteral implants due to their non-toxicity and biocompatibility (Guse et al. 2006; Blasi et al. 2007). The commonly used method for the preparation of triglyceride monolithic implants is compression (Vogelhuber et al. 2003; Guse et al. 2006; Guse et al. 2006; Koennings et al. 2006). Solid lipids, such as triglycerides, can also be produced into implants by hot-melt extrusion. For polymers, hot-melt extrusion is normally processed at a temperature of 30-60°C above their glass transition temperatures (T_g) (Repka et al. 2002). By contrast, the operating temperature of solid lipids should be adjusted to approximately 10°C below their melting points (T_m) (Reitz and Kleinebudde 2007; Krause et al. 2009). Thus, the development of a polymer based drug release systems with the addition of a lipid would be a new challenge regarding the operation of the process. The processing temperature has to be carefully optimized when both polymer and lipid are introduced to a formulation for implants.

Polymer blend is a simple method to achieve new polymer properties for meeting requirements in several applications, to combine the positive features of different polymers

and to avoid the disadvantages of each polymer (Bae and Kim 1993; DeMeuse 1995; Domb et al. 1999). Properties of polymer blends are dependent on miscibility and phase behavior. Miscibility of polymer blends can be basically classified into miscible and immiscible blends. A miscible polymer blend is considered as a homogeneous system (DeMeuse 1995). A single glass transition temperature (T_g) can be detected when using differential scanning calorimetry, while two or more T_g are observed for immiscible blends (Jorda and Wilkes 1988; Cameron et al. 2002; Pillin et al. 2006). In addition to two distinct T_g, two separated phases, or polymer emulsion occurs when polymers are immiscible (Roths et al. 2002; Lipatov 2006).

Polymer blends have been introduced for the preparation of controlled release coating, microparticles and implants. The advantages of polymer blends for controlled release applications include easy fabrication, improvement of properties (such as hydration, drug release) and increase in drug loading (Bae and Kim 1993; Siepmann et al. 2008). To improve drug release profiles from biodegradable microparticles and implants, blends of PLGA and/or PLA polymers have been created (Domb et al. 1999; Blanco-Príeto et al. 2004; Booth et al. 2005; Matsumoto et al. 2005; Luan and Bodmeier 2006). The initial burst release could be suppressed and the release profiles were changed by blending PLGA with different molecular weight PLGA, or different lactide:glycolide ratios (Blanco-Príeto et al. 2004; Booth et al. 2005; Luan and Bodmeier 2006). The second burst release could be prevented, and the lag-time of the drug release from PLA was reduced by the blends of high and low molecular weight PLA and blending with PLA-poly(mandelic acid), respectively (Domb et al. 1999; Kunou et al. 2000). Therefore, PLGA blending with PLA is likely to be a useful new strategy to modify the release pattern and mechanism of biodegradable implants prepared by hot-melt extrusion.

The objectives of this study were to investigate the effect of incorporating PEG on the thermal, mechanical, physical and drug release properties of PLGA hot-melt extrudates, to modify the release profiles of PLGA hot-melt extruded implants from the degradation-dependent (bi- or triphasic release) to a continuous release profile by the addition of tristearin, and to modify drug release profiles of PLGA implants by using a polymer blend technique. The influences of a change in the molecular weights on the T_g of PLGA and recrystallization of PEG were determined. Small molecular weight drugs with different water solubilities and

partition coefficients (tramadol HCl, dexamethasone sodium phosphate and diazepam) were used as model drugs.

3.3.2. Results and discussion

The thermal stability of PLGA (502H and 503H) and PLA were studied prior to preparing PLGA/PLA blended implants using hot-melt extrusion, since hot-melt extrusion involves a high processing temperature. PLGA and PLA start to decompose at about 200°C (Fig. 3.17). At temperatures above 200°C, the mass of PLGA and PLA decreased dramatically. The maximum rate of mass loss (T_{max}) was approximately 300°C for PLGA and 315°C for PLA. From this result, the polymers were thermally stable at the used extrusion temperature (60 - 100°C).

PEG with an average molecular weight equal to 1500 was selected as a hydrophilic additive, because this is the lowest molecular weight PEG which is in the solid-state. Greater heat stability and decreased weight loss due to evaporation during the hot-melt extrusion process are benefits of using a solid material as a plasticizer. Mixing a polymer with a solid-state substance is easier when compared to a viscous liquid; a higher homogeneity of mixture can be obtained. Homogeneous mixing leads to stable mass flow during feeding of the mixture and results in uniformity of the final extruded product (Wu and McGinity 2003; Schilling et al. 2007). In addition, PEG is accepted for parenteral use (Zhu et al. 1990), thus it can be an appropriate additive for implant drug delivery systems.

The solubility parameters of PLGA and PEG were considered in order to predict the miscibility between PLGA and PEG. The miscibility of two substances has a tendency to be dependent on the similarity of the solubility parameters. From the literature, the solubility parameter of PLGA is in the range of 19.9 – 23.1 $MPa^{1/2}$ (Shively et al. 1995; Thomasin et al. 1998; Schenderlein et al. 2004) and the solubility parameter of PEG 1500 is in the range of 23.1 – 23.9 $MPa^{1/2}$ (Otozai 1976; Pasquali et al. 2008). If the difference of solubility parameters is less than 7.0 $MPa^{1/2}$, miscibility in molten state is probable (Greenhalgh et al. 1999; Ghebremeskel et al. 2007). Therefore, miscibility between PLGA and PEG 1500 was expected.

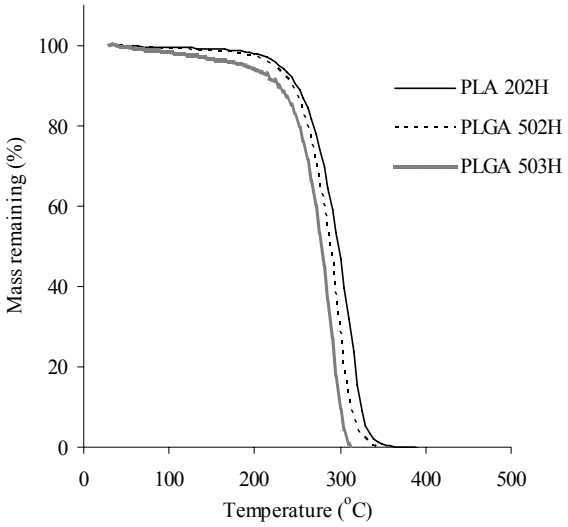


Fig. 3.17. Thermogravimetric mass loss curves of PLGA 502H, 503H and PLA 202H

The addition of PEG 1500 into PLGA hot-melt extrusion reduced the maximum torques (Table 3.7). In the presence of the model drug, PEG 1500 was also able to decrease the torque values of the polymer system (Table 3.7). The melt viscosity, as represented by the maximum torques, is a good indicator for evaluating the processibility of hot-melt extrusion. The decrease in the melt viscosity by PEG 1500 improved the processibility of PLGA hot-melt extrusion, and thus the extrusion temperature could be reduced. The hot-melt extrusion can be operated at temperatures as low as 55-60°C for PLGA 502H with 10% w/w PEG 1500.

PLGA hot-melt extrudates without the additive were rigid and brittle. The addition of 10% w/w PEG 1500 into PLGA extrudates resulted in more flexible PLGA hot-melt extrudates. The percent elongation at break was increased by the presence of the additive (Table 3.8). Although the tensile strength of PLGA 503H hot-melt extrudate was decreased, as is the usual effect for improving mechanical properties by an additive, the tensile strength of PLGA 503H hot-melt extrudate was increased (Table 3.8). This was attributed to the high rigidity of PLGA 502H hot-melt extrudate. The extrudate was always broken after starting the test.

Table 3.7. Effect of PEG 1500 on maximum torques of PLGA hot-melt extrudates

Model drug (10% w/w)	PEG 1500 (% w/w)	Maximum torque (Nm)	
		PLGA 502H	PLGA 503H
-	0	0.21	0.84
	5	0.13	0.32
	10	0.10	0.16
	15	0.10	0.14
	20	0.08	0.10
Tramadol HCl	0	0.39	1.26
	10	0.12	0.18
Diazepam	0	0.30	0.65
	10	0.10	0.16

Table 3.8. Effect of PEG 1500 on the mechanical properties of PLGA hot-melt extrudates

PLGA	PEG 1500 concentration (%w/w)	Tensile strength (psi)	Elongation at break (%)
502H	0	5 ± 7	0
	10	290 ± 88	41.18 ± 11.90
503H	0	2938 ± 129	1.98 ± 0.52
	10	1074 ± 164	121.89 ± 50.06

Following hot-melt extrusion of PLGA and PEG 1500 (10% w/w), the melting peak of the crystalline PEG 1500 disappeared and a single T_g was observed in the DSC thermogram (Fig. 3.18). It can be hypothesized that 10% w/w PEG 1500 was dissolved or molecularly dispersed in the PLGA hot-melt extrudates. A shift in the T_g of PLGA from approximately 40°C to 20°C was detected for PLGA hot-melt extrudate containing 10% w/w PEG 1500, while this finding was not observed with the physical mixture (Fig. 3.18). No significant change in the T_g and only a smaller crystalline peak of PEG 1500 was detected for the physical mixture. PEG 1500 was possibly partially dissolved in PLGA, but a homogeneous blend was not obtained for the physical mixture.

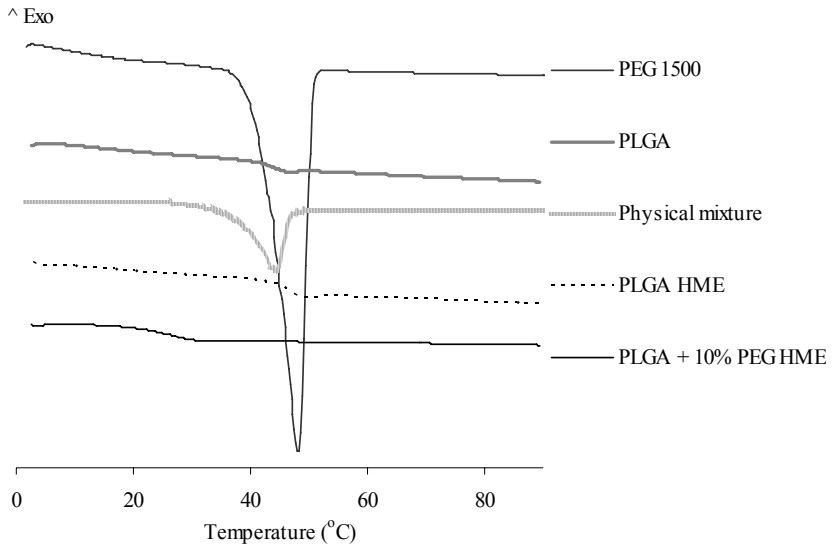


Fig. 3.18. DSC thermogram of PEG 1500, PLGA 503H powder, their physical mixture of 10% w/w PEG 1500, PLGA 503H hot-melt extrudate and PLGA 503H hot-melt extrudate containing 10% w/w PEG 1500

Several theoretical and empirical equations have been used to estimate the T_g of compatible polymer blends. A widely used equation for predicting T_g of blend systems is the Gordon-Taylor equation. The T_g of the blend system can be calculated using the equation as follows (Katkov and Levine 2004):

$$T_g\,(K) = \frac{W_1 T_{g1} + kW_2 T_{g2}}{W_1 + kW_2} \qquad (3.1)$$

W_1 and W_2 are the weight fractions of the two components, and T_{g1} and T_{g2} represent the T_g value of each component. The Gordon-Taylor coefficient (k) was originally based on polymer free volume theory. A simple equation including the true density has been established afterwards in order to determine k (Katkov and Levine 2004).

$$k = \frac{\rho_1 T_{g1}}{\rho_2 T_{g2}} \qquad (3.2)$$

Another equation for the prediction of T_g of a polymer system is the Fox equation (Fox 1956). It has been widely used when the system is compatible, and weak interaction is observed (Pillin et al. 2006). The equation is as follows:

$$\frac{1}{T_g} = \frac{W_1}{T_{g1}} + \frac{W_2}{T_{g2}} \qquad (3.3)$$

T_{g1} and T_{g2} refer to the T_g of a pure polymer or an additive in Kelvin, whereas W_1 and W_2 are the weight fraction of each component.

The T_g of PLGA 503H determined in this investigation was 44.4°C (Fig. 3.19). The true density of PLGA 503H was 1.5804 g/ml (Blasi et al. 2005). PEG 1500 has a T_g of -52.86°C and a true density of 1.062 g/ml (Thies and Kleinebudde 2001). These parameters were used to calculate the theoretical T_g of the mixtures by the Gordon-Taylor and Fox equations. The experimental and predicted T_g of the mixtures were plotted against the PEG concentration. The T_g was inversely proportional to the PEG the concentration (Fig. 3.19). A decrease in T_g was observed with an increase in the PEG concentration. The experimental data did not correlate well with the prediction from the Fox equation. However the plot between the experimental T_g of PLGA in the presence of PEG 1500 showed a good agreement with the theoretical Gordon-Taylor prediction (Fig. 3.19). The agreement only between the Gordon-Taylor equation and the experimental data could be explained by the increased number of parameters in this equation. It indicates that only using the weight fraction (as in the Fox equation) was insufficient to predict the experimental T_g of the PLGA/PEG 1500 blends.

The improvement of processibility due to the reduced melt viscosity, modification of mechanical properties and the suppression of T_g as a function of PEG 1500 concentration demonstrated the plasticizing effect PEG 1500 has on PLGA. The single T_g of PLGA and the disappearance of the crystalline PEG 1500 pattern with 5 and 10%w/w PEG (Fig. 3.20) indicated the miscibility of the blends of the polymers. PEG 1500 chains spread themselves in-between the polymer chains. Two different polymers which are miscible pack less well than the homopolymer, providing more mobility for the polymer molecules and resulting in decreasing melt viscosity during extrusion and enhancement of mechanical properties (Elias 1997; Rahman and Brazel 2004; Schilling et al. 2007).

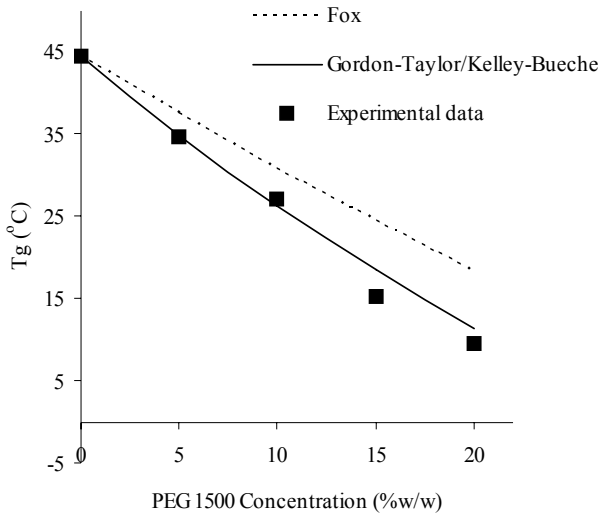


Fig. 3.19. T_g of PLGA 503H as a function of PEG 1500 concentration

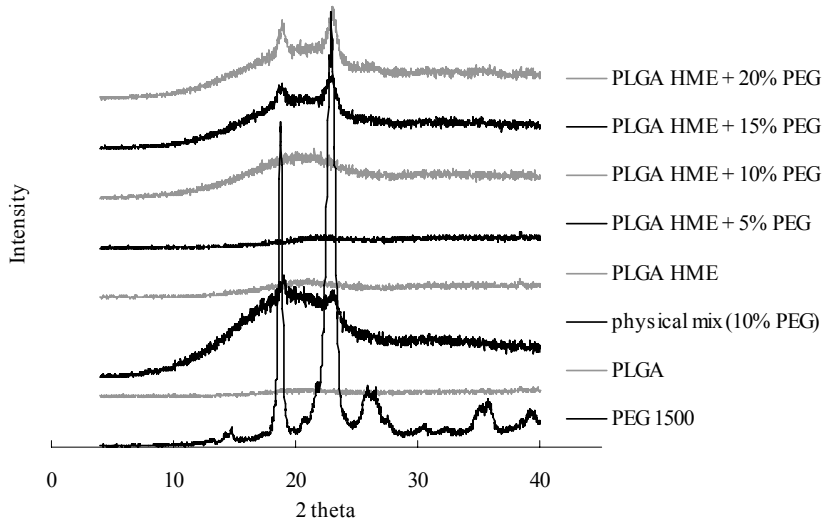


Fig. 3.20. X-ray powder diffraction of PEG 1500, PLGA 503H powder, their physical mixture of 10% w/w PEG 1500, PLGA 503H hot-melt extrudate and PLGA 503H hot-melt extrudate containing 10% w/w PEG 1500 (3 days after processing)

Upon storage at ambient conditions, PLGA hot-melt extrudate containing 15% w/w PEG 1500 became turbid (a solid dispersion). The result for the extrudate containing 20% w/w PEG 1500 was not clear since it was cooled down to room temperature. Therefore the crystalline PEG 1500 peak was observed for DSC thermogram immediately after hot-melt

extrusion (Table 3.9). In the case of PLGA hot-melt extrudate containing 15% w/w PEG 1500, the crystalline PEG 1500 peak appeared after 3 days of storage (Table 3.9). The recrystallized PEG 1500 was also found from X-ray diffraction (15 and 20% w/w PEG 1500) (Fig. 3.20). Recrystallization of PEG altered the T_g as a function of time (Table 3.9), with the T_g increasing on storage. For 5 and 10% PEG the T_g was constant throughout the study, and recrystallization of PEG 1500 could not be detected. PEG 1500 itself was highly crystallizable. During quenching, 96.30% of the crystalline PEG 1500 was recrystallized after cooling the molten mixture. Therefore it tends to be easily recrystallized upon storage, especially when the PEG 1500 concentration exceeds the solubility limit. A similar result for the recrystallization of PEG at high PEG concentration blended with poly(lactide) (PLA) has been reported. Over time, blends of 20% w/w and more PEG and PLA were unstable because of recrystallization of the PEG (Hu et al. 2003). The recrystallization of PEG 1500 upon storage occurred with PLGA 502H containing 15 and 20% w/w PEG, hence the solubility of PEG 1500 in PLGA 502H was calculated using the melting enthalpy of excess PEG 1500 at day 3 and 5. The solubility was approximately 13% w/w. Therefore, the recommended concentration of PEG 1500 as a plasticizer for PLGA should not exceed 13% w/w, which relates to the stability issue.

The T_g of PLGA hot-melt extrudates were dependent on the molecular weight and the T_g of PEG (Table 3.10). The plasticizing effect was strongest for the lowest molecular weight PEG, whereas the T_g of PLGA containing PEG 1500, 3350 and 4000 were in the same range and are indistinguishable. The smaller T_g of the PLGA hot-melt extrudate containing PEG 400 was attributed to the liquid state of PEG 400 and the fact that PEG 400 had the lowest T_g of the PEG samples (Table 3.10). The effect of the PEG molecular weight on PLGA was similar to that of poly(L-lactic acid) (L-PLA). With the addition of PEG, the T_g of L-PLA could be differentiated into three groups, based on the molecular weight of the PEG. PEG was classified into low (PEG MW 400), intermediate (PEG MW 1500-3400) and high (PEG MW 10,000) molecular weights. The T_g of L-PLA were in the same range as those with the incorporation of the intermediate molecular weight PEGs (Baiardo et al. 2003). PEG 1500, 3350 and 4000 are also considered to have intermediate molecular weights. Therefore the influence of PEG 1500, 3350 and 4000 on the PLGA T_g could not be differentiated.

Table 3.9. Changes in T_g of PLGA 502H hot-melt extrudates and observation of crystalline PEG 1500 peak as a function of time

PEG 1500 concentration (% w/w)	Time (d)	T_g first run (°C)	T_g second run (°C)	Observation of crystalline PEG 1500 peak
0	0	42.4	39.8	–
5	0	27.6	26.4	–
	1	27.8	26.8	–
	3	27.6	26.8	–
10	0	19.3	18.4	–
	1	18.5	17.3	–
	3	18.9	17.6	–
15	0	9.4	8.0	–
	1	18.8	17.8	–
	3	12.3	8.8	+
20	0	0.6	0	+
	1	42.2	0	+
	3	43.0	0.4	+

+ observed; – not observed

Table 3.10. Effect of PEG molecular weight on T_g of PLGA hot-melt extrudates containing 10% w/w PEG

PEG		T_g of hot-melt extrudates (°C)	
Average molecular weight	T_g (°C)	PLGA 502H	PLGA 503H
400	-65.5	12.6	13.4
1500	-52.9	18.4	23.8
3350	-43.4	19.0	24.8
4000	-49.2	18.7	23.8

Without PEG 1500 as a plasticizer, the water uptake of PLGA extrudates was slow during the initial period (the first 3 days) followed by rapid water absorption. With the incorporation of PEG 1500, the rate of water uptake was proportional to the PEG concentration (Fig. 3.21a). An increased water uptake with increasing PEG concentration was observed. PEG is a hydrophilic water-soluble molecule. A greater amount of PEG in the extrudates caused greater hydrophilicity of the blends between PLGA and PEG 1500, and thus higher water uptake. In contrast to water uptake, no significant effect of PEG 1500 on the mass loss of PLGA extrudates was seen (Fig. 3.21b). The mass loss of PLGA can be correlated to the polymer degradation. The addition of PEG 1500 did not affect PLGA degradation. PLGA degradation depends on the temperature and the T_g of the PLGA. A faster degradation rate occurs at higher temperatures, particularly above T_g of the polymer (Kranz et al. 2000; Richards Grayson et al. 2005). All PLGA hot-melt extrudates were probably in a rubbery state because the incubation temperature (37°C) was already close to the T_g of PLGA without the plasticizer, and above the T_g of PLGA hot-melt extrudates containing 10 and 20% w/w PEG 1500. Therefore, no influence of the plasticizer was observed.

The release profiles of tramadol HCl and diazepam from PLGA implants prepared by hot-melt extrusion were sigmoidal curves (Fig. 3.22). The drug releases were slow during the early stage. The drugs were released by diffusion through the dense PLGA matrix as a result of the hot-melt extrusion process. Subsequently, the drug release rates dramatically increased when the onset of mass loss was reached. The significant increase in the rate of drug release corresponded to the rapid increase in mass loss after 7 days (Fig. 3.21b and Fig. 3.22) for PLGA 503H (mass loss data of PLGA 502H not shown). The lag-times of the drug releases from PLGA 503H implants were longer than those from PLGA 502H implants (Fig. 3.22) due to the longer degradation and onset of mass loss of PLGA 503H as a result of the higher inherent viscosity (PLGA 503H, 0.32-0.44 dl/g; PLGA 502H, 0.16-0.24 dl/g) which are related to the larger moleculer weight. The addition of 10% w/w PEG 1500 into PLGA implants containing 10% w/w tramadol HCl resulted in a decrease in the initial burse release (Fig. 3.22a). The decrease in the initial burst release by the addition of the plasticizer was previously reported in the literature (Tan et al. 2004; Tang and Singh 2008). This effect could be explained by the denser matrix of PLGA due to the presence of the plasticizer. In comparison with tramadol HCl (solubility 793.5 ± 97.8 mg/ml in phosphate buffer pH 7.4 at

ambient temperature), no burst release was found for diazepam (Fig. 3.22b) due to its low water solubility (0.072 ± 0.005 mg/ml in phosphate buffer pH 7.4 at 37°C).

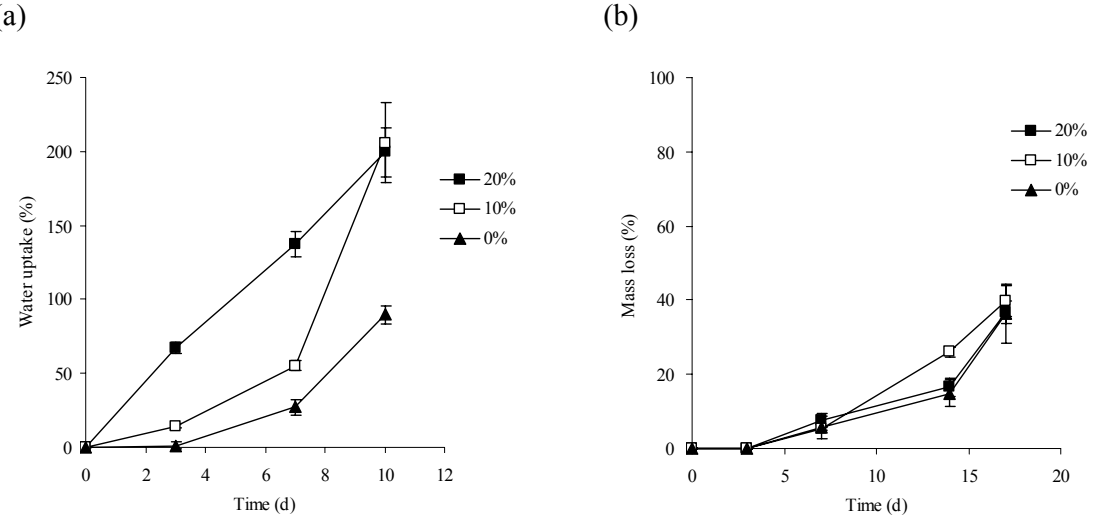


Fig. 3.21. Effect of PEG 1500 on (a) water uptake and (b) mass loss of PLGA 503H hot-melt extrudates

A biocompatible material, a triglyceride, was chosen to modify the drug release from PLGA implants prepared by hot-melt extrusion, due to the safety and wide use of triglycerides for implantable delivery systems (Mohl and Winter 2004; Guse et al. 2006). For hot-melt extrusion of a polymer, an extrusion temperature above the T_g of the polymer is required (Repka et al. 2002). Without triglycerides, PLGA could be extruded using a temperature above 75°C. In contrast to the polymer, the triglyceride has to be extruded at temperatures below the T_m of the triglyceride (Reitz and Kleinebudde 2007; Krause et al. 2009). Due to the difficulty of adjusting the extrusion temperature, a triglyceride with a melting range close to the processing temperature of PLGA, tristearin (T_m 70-73°C), was selected. In addition to the concerns about the melting point of the triglyceride, the melt viscosity in combination with the T_g of PLGA had to be optimized in order to process the blends using a low extrusion temperature. 10% w/w PEG 1500 was added for this purpose. The T_g of PLGA was reduced by approximately 20°C and the maximum torque was decreased by 0.11 Nm for PLGA 502H and 0.68 Nm for PLGA 503H. Finally, the blends of PLGA and 20-40% w/w tristearin could be successfully used to prepare by implants by hot-melt extrusion at temperatures of 55-65°C. Above 40% w/w tristearin, the system could not be processed by hot-melt extrusion.

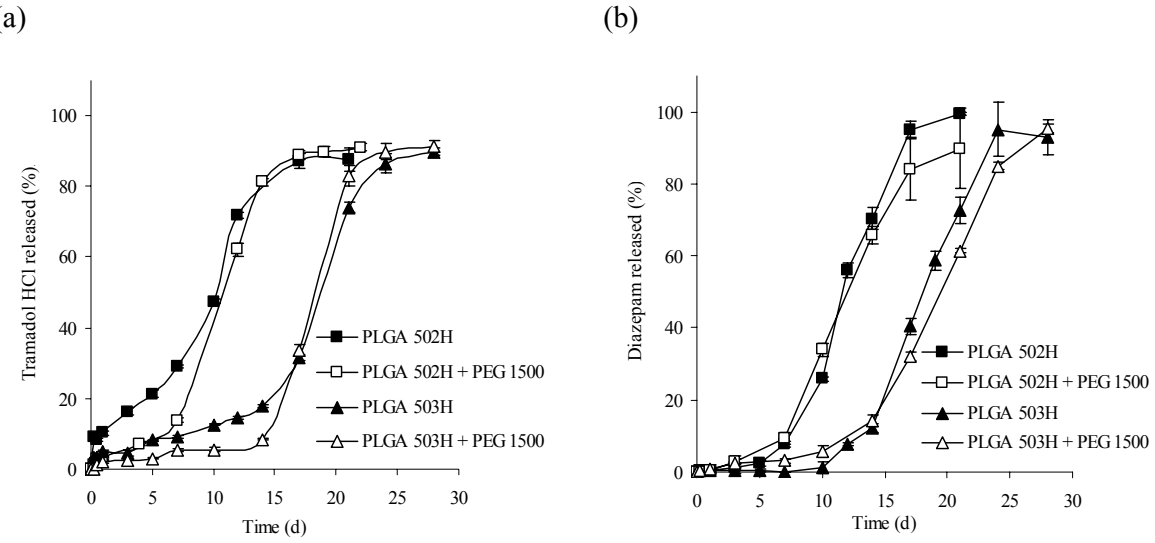


Fig. 3.22. Drug release from PLGA hot-melt extrudates with/without 10% w/w PEG 1500; (a) tramadol HCl and (b) diazepam (10% w/w)

PLGA hot-melt extruded implants without the addition of tristearin were transparent, cylindrical, and had a smooth surface. The implants became more turbid and had rougher surfaces with the presence of tristearin in the formulas. With 20% w/w tristearin, the implant was milky. It became completely opaque when the tristearin concentration was increased to 40% w/w. The appearance of the PLGA/tristearin implants can be explained by the use of a lower processing temperature than the melting point of tristearin (70-73°C). Tristearin remained in the crystalline form, but was softened. The turbid implants and rough surface of the blend implants was caused by the nature of tristearin, which was incompletely molten.

A slight increase in maximum torques by the addition of tristearin was detected, and thus an increase in the melt viscosity during hot-melt extrusion (Table 3.11). The highest maximum torque was obtained from the batches containing 20% w/w tristearin. With increasing tristearin concentration (above 20% w/w), the maximum torques tended to decrease. Two factors, the presence of solid content and the amount of PLGA polymer, played a role on the resulting maximum torques of the PLGA/tristearin blends. The addition of tristearin led to the presence of solid content in the mixture, resulting in an increase in the maximum torques. On the other hand, the reduction of maximum torques with increasing tristearin concentration above 20% w/w was caused by a decrease in PLGA content. The incorporation of 10% w/w

diazepam into the implants was revealed to slightly decrease maximum torques in comparison with no drug loading (Table 3.11). This can be explained by the smaller amounts of PLGA/tristearin blends in the barrel of the hot-melt extruder.

Table 3.11. Maximum torques (Nm) of PLGA 502H with different Dynasan 118 concentration containing 10% w/w PEG 1500 during hot-melt extrudates at 65 °C

Tristearin concentration (%)	No drug loading (Nm)	10% w/w diazepam loading (Nm)
0	0.10	0.10
20	0.17	0.16
30	0.15	0.12
40	0.13	0.11

When using hot-melt extrusion as a preparation method, solid lipids undergo mechanical and thermal stress. Polymorphic transformation of solid lipids may occur during this process (Reitz and Kleinebudde 2007). Hence, the solid state of tristearin was investigated by DSC before and after hot-melt extrusion to verify the stability and miscibility of the PLGA/tristearin mixture. The bulk tristearin revealed an endothermic peak at 73.2 °C as a result of the melting of the crystalline β-form (Fig. 3.23) (Mohl and Winter 2004). The DSC thermograms of the physical mixture and the hot-melt extrudates of PLGA containing 30% w/w tristearin and 10% w/w PEG 1500 were similar except the melting peak at 49.6°C from the physical mixture. The melting peak at 49.6°C was attributed to the melting peak of PEG 1500. After hot-melt extrusion, PEG 1500 dissolved or dispersed molecularly in PLGA resulting in the absence of the crystalline PEG 1500 peak, and a decrease in the T_g of PLGA (due to the plasticizing effect). The endothermic peak of tristearin (73.5 °C) was observed from the hot-melt extrudate at a similar temperature as the bulk tristearin (Fig. 3.23). For all tristearin concentrations, DSC thermograms of tristearin after hot-melt extrusion demonstrated similar features. Changes in the solid state of tristearin were not found after the PLGA/tristearin blends were prepared by hot-melt extrusion in the range of 55-65°C. Moreover, the blend or mixture of plasticized PLGA and tristearin was immiscible. The mixture after hot-melt extrusion showed both the T_g of PLGA and the melting peak of tristearin.

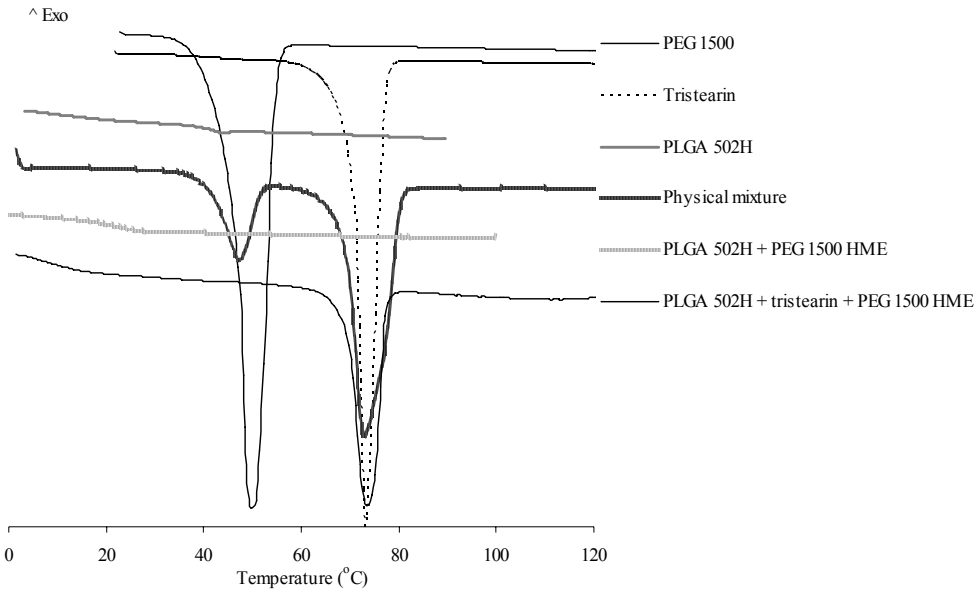


Fig. 3.23. DSC thermogram of PLGA 502H hot-melt extrudate containing 30%w/w tristearin and 10% w/w PEG 1500 as a plasticizer.

Diazepam release from PLGA implants without tristearin was biphasic (Fig. 3.24). A slow release in the initial period was observed, followed by a faster release due to bulk degradation of PLGA. The release increased dramatically at the starting period of PLGA mass loss (approximately 15% w/w after day 7 for PLGA 502H and day 14 for PLGA 503H). In contrast to PLGA implants, the profiles were changed and diazepam releases were faster when tristearin was added (Fig. 3.24). A continuous release with no initial and second burst release was achieved with 30% and 40% w/w tristearin. The release from implants containing 30% and 40% w/w tristearin were completed earlier than the implants without tristearin, with the exception of the 30% w/w tristearin/PLGA 502H implant. Subsequently, diazepam release from PLGA 502H/tristearin and PLGA 503H/tristearin were compared. According to the longer degradation period of PLGA 503H, a longer lag-time was found for the PLGA 503H implant, and a more prolonged drug release was obtained from the PLGA 503H/tristearin blend implants (Fig. 3.24b).

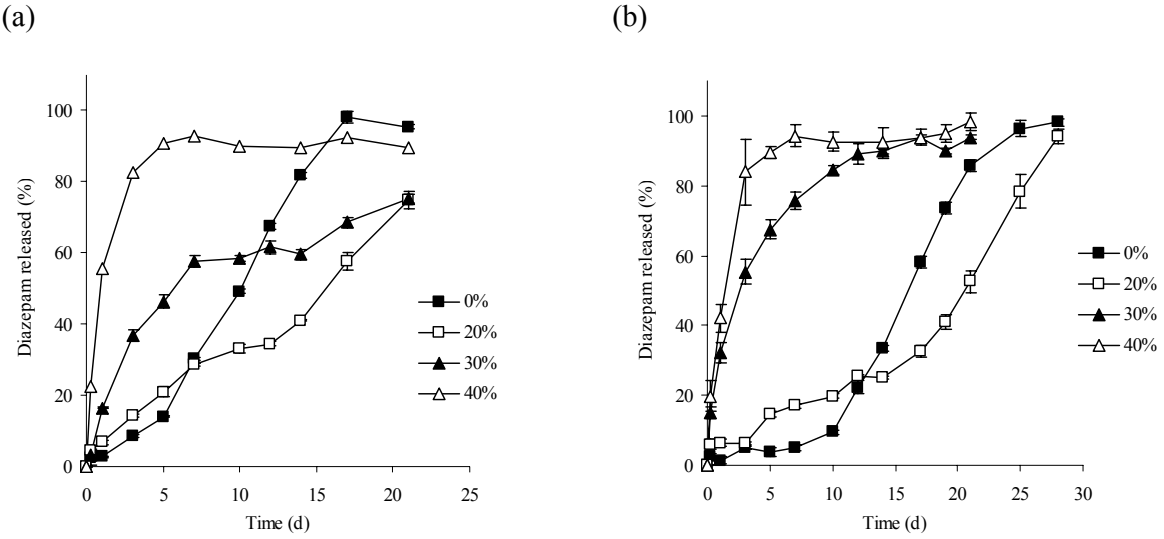


Fig. 3.24. Diazepam release from PLGA/tristearin implants containing 0-40 % w/w tristearin and 10% w/w drug loading (a) PLGA 502H and (b) PLGA 503H

Fitting drug release profiles to theoretical equations is a method to explain the release mechanism. Eq. 3.4 models a degradation-controlled mechanism (Gallagher and Corrigan 2000):

$$\ln \frac{x}{(1-x)} = kt + kt_{max} \qquad (3.4)$$

Where x is the fraction of drug released at time t, k is a rate constant and t_{max} is the time to the maximum drug release rate.

The Korsmeyer-Peppas model was used for diffusion-controlled release (Korsmeyer et al. 1983):

$$\frac{M_t}{M_\infty} = kt^n \qquad (3.5)$$

Where M_t is the drug released at time t, M_∞ is the quantity of drug release at infinite time and k is a kinetic constant. For a cylindrical shape, n equal to 0.45 indicates a diffusion-controlled mechanism.

Another equation to describe a diffusion-controlled release mechanism is the Higuchi model. The Higuchi model is applied when a drug is dispersed homogeneously in a polymer matrix. The relationship is as follows (Higuchi 1961; Kunou et al. 2000):

$$Q = \sqrt{D(2W - C_s)\,C_s t} \qquad (3.6)$$

Where Q is amount of drug released in time t, D is the drug diffusion coefficient in the matrix, C is the total drug amount per unit volume of matrix, C_s is the drug solubility and W is total amount of drug per unit volume of matrix. When C >> Cs, the relationship can be shortened to the following equation:

$$Q = \sqrt{2DWC_s t} \qquad (3.7)$$

From the above equation, the amount of drug released is proportional to the square root of time. Therefore, it is possible to simplify the equation as follows (known as the simplified Higuchi model:

$$Q = K_H t^{\frac{1}{2}} \qquad (3.8)$$

In this equation, K_H refers to Higuchi dissolution constant.

Diazepam release from PLGA implants was fit to the equation of the degradation-controlled mechanism (Eq. 3.4) giving coefficient of determinations (R^2) equal to 0.9909 and 0.9902 respectively (Table 3.12). When tristearin was added to PLGA implants the diazepam releases did not correlate well with the degradation-controlled equation, resulting in a progressive decrease of R^2. The minimum R^2 was obtained with 30% w/w tristearin for PLGA 502H and 40% w/w tristearin for PLGA 503H blend implants. By contrast, the release profiles of the implants containing 30% and 40% w/w tristearin gave a good fit with the Korsmeyer-Peppas model (Eq. 3.5) (R^2 between 0.9622-0.9967) and the Higuchi model (Eq. 3.8) (R^2 between 0.9702-0.9974) (Table 3.12). Thus, the profiles were changed from a largely

degradation-controlled mechanism to a diffusion-dependent release due to the addition of 30-40% w/w tristearin.

Table 3.12. Curve fitting results for degradation controlled mechanism, Korsmeyer-Peppas and Higuchi model

Tristearin concentration (% w/w)	R^2					
	Degradation controlled		Korsmeyer-Peppas		Higuchi	
	PLGA 502H	PLGA 503H	PLGA 502H	PLGA 503H	PLGA 502H	PLGA 503H
0	0.9909	0.9902	0.7422	0.5050	0.7780	0.5365
20	0.9396	0.9163	0.9042	0.8130	0.9263	0.8399
30	0.6988	0.9065	0.9622	0.9967	0.9702	0.9974
40	0.8661	0.8606	0.9749	0.9775	0.9612	0.9777

Water uptake, mass loss, apparent partition coefficient and SEM were studied in order to clearly understand the drug release mechanisms from PLGA and PLGA/tristearin blend implants. Water uptake and mass loss between PLGA and PLGA/tristearin blend implants could not be differentiated until the 14th day of these experiments (Fig. 3.25). A higher water uptake by the PLGA 502H implant at day 14 was detected because of the higher acid by-product from the PLGA in the implant. The water uptake and mass loss results of both PLGA implants were similar. The change in the release mechanism due to the addition of tristearin was effectively explained by the K_{app} and SEM results (Table 3.13 and Fig. 3.26). The K_{app} of 30% w/w tristearin/PLGA implants increased as a function of time, resulting in the continuous diffusion and release of diazepam (Table 3.13). On the other hand, the biphasic releases from the implants without tristearin were obtained due to a sudden increase in K_{app} at the onset of the PLGA mass loss (day 7 for PLGA 502H and day 14 for PLGA 503H) (Table 3.13). Similar to K_{app}, the cross section from SEM supported the release mechanism of the implants. Without tristearin, the cross section of PLGA implant showed diazepam particles among a smooth and dense structure (Fig. 3.27a). An increase in the porosity of implants was observed with increasing tristearin concentration (Fig. 3.27b-c). The pores inside the PLGA/tristearin implants were created by partially molten tristearin during hot-melt extrusion (Reitz and Kleinebudde 2007). Diazepam could be released by diffusion through the porous

structure, and this resulted in continuous drug releases when tristearin was added to the PLGA implants.

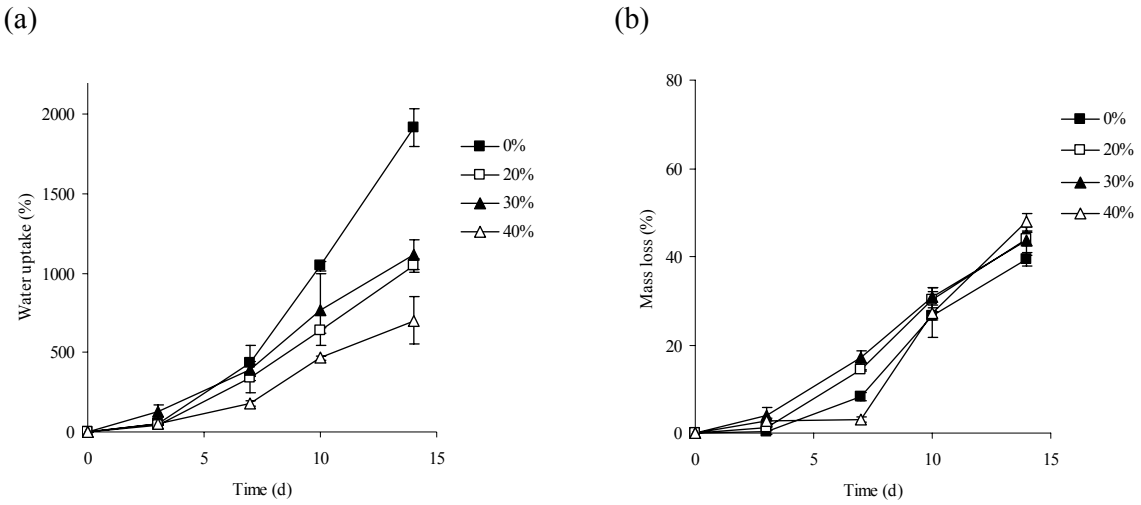


Fig. 3.25. Physical properties of PLGA 502H/tristearin implants containing 0-40 % w/w tristearin (a) water uptake and (b) mass loss

Table 3.13. K_{app} of diazepam between PLGA 502H and 503H implants and the release medium

Time (d)	K_{app} ($\times 10^{-4}$)			
	PLGA 502H		PLGA 503H	
	0% w/w tristearin	30% w/w tristearin	0% w/w tristearin	30% w/w tristearin
1	2.5 ± 0.2	3.7 ± 0.8	0.68 ± 0.2	3.9 ± 1.0
3	8.7 ± 0.3	7.6 ± 0.9	2.6 ± 0.3	9.7 ± 0.7
7	42.3 ± 3.6	17.0 ± 1.4	8.9 ± 1.7	14.5 ± 0.4
10	64.8 ± 6.0	68.1 ± 8.9	19.3 ± 0.2	19.6 ± 1.5
14	-	-	80.4 ± 0.7	34.2 ± 1.9

Drugs with different water solubility and log $K_{o/w}$ were incorporated into 30% w/w tristearin/PLGA 502H implants in order to investigate the effect drug properties on drug releases. The drug release of the three model drugs showed similar continuous release profiles (Fig. 3.27). Dexamethasone salt and tramadol HCl releases were faster than the diazepam release. The faster release of dexamethasone salt and tramadol HCl was attributed

to the higher water solubility and lower partition coefficient of these compounds (Table 3.14). A lower drug partition into the lipid part of the implants occurred with dexamethasone salt and tramadol HCl. Upon exposure to the release medium, the highly water-soluble drugs could be easily dissolved and released through the water-filled pores of the porous tristearin/PLGA implants (Fig. 3.26) resulting in a faster release compared to diazepam.

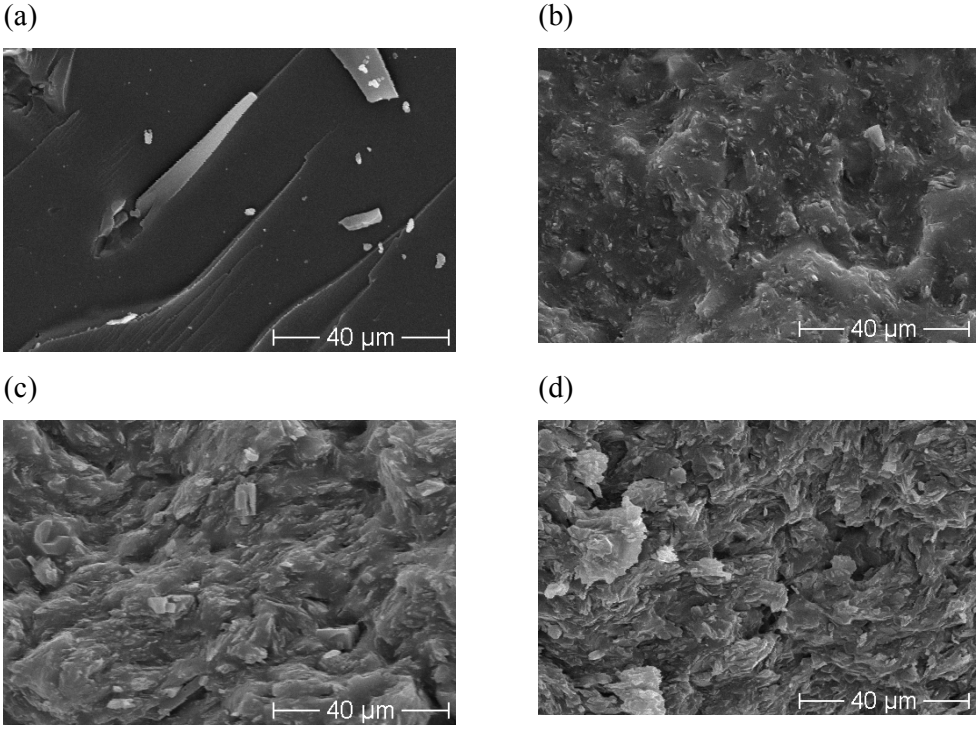


Fig. 3.26. Cross section of PLGA 502H/tristearin implants (600× SEM magnification) (a) 0% (b) 20% (c) 30% and (d) 40% w/w tristearin

Table 3.14. Solubility and partition coefficient (log $K_{o/w}$) values

Drugs	Solubility (mg/ml)	Partition coefficient
Tramadol HCl	793.5 ± 97.8 [(a)]	-1.06 ± 0.21
Dexamethasone sodium phosphate	433.2 ± 13.7 [(a)]	-1.56 ± 0.09
Diazepam	0.2 ± 0.02 [(b,c)]	2.70 [(d)]

[(a)] at room temperature; [(b)] at 37°C; [(c)] with the addition of 0.1% w/v SDS

[(d)] (Loftsson and Hreinsdóttir 2006)

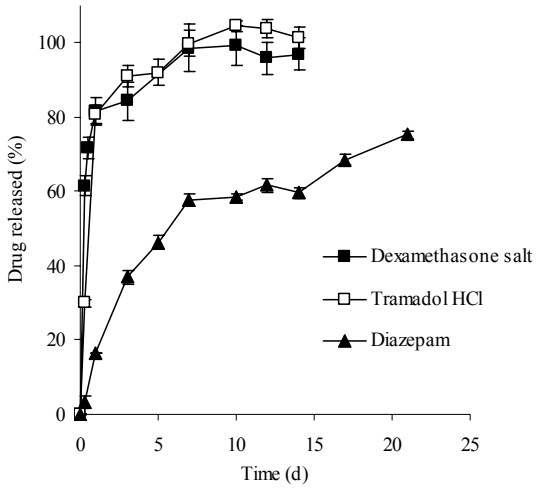


Fig. 3.27. Comparison of drug releases from PLGA 502H implants containing 30%w/w Dynasan 118 and 10% w/w drug loading

Drug release from controlled-release systems based on PLGA and PLA polymer showed typically bi- or triphasic release profiles (Dorta et al. 2002; Wang et al. 2002; Luan and Bodmeier 2006). A continuous release was difficult to achieve due to the bulk degradation of the polymers. PLGA blended with PLA was selected as a method to modify the release profiles from PLGA implants, because successful modifications of drug releases have been obtained previously by blending PLGA or PLA with a different molecular weight polymer (using a similar polymer) and blending PLA with other biodegradable polymers (Domb et al. 1999; Kunou et al. 2000; Booth et al. 2005; Luan and Bodmeier 2006).

During hot-melt extrusion, low maximum torque values of PLGA 502H/PLA blends in various ratios were obtained (Table 3.15) and thus they have a low melt viscosity. There was no difference in the maximum torque found between PLGA 502H, PLA 202H and the blends in various ratios. The torque values during hot-melt extrusion were dependent upon the inherent viscosity of the polymers. The inherent viscosity values for PLGA 502H and PLA 202H are low and similar (0.16-0.24 dl/g), hence the similarity in the maximum torques. For the blends using PLGA 503H instead of PLGA 502H, a higher inherent viscosity (0.32-0.44 dl/g) of PLGA 53H had an impact on the maximum torques. The maximum torque of the PLGA 503H/PLA (2:1) blends was higher compared to the blends in other ratios, due to it having the highest PLGA 503H content (Table 3.15).

Table 3.15. Recorded maximum torque values during hot-melt extrusion of PLGA 503H/ 502H/ PLA 202H blend

PLA 202H/PLGA ratio	Maximum torque (%w/w)			
	PLGA 503H	PLGA 502H		
		PEG 1500 (% w/w)		
		0	5	10
0:1	0.84	0.21	-	-
1:2	0.26	0.22	-	-
1:1	0.20	0.16	0.10	0.09
2:1	0.18	0.15	-	-
1:0	0.16	0.16	-	-

The blends of PLGA and PLA were immiscible. The immiscibility of the polymer blends was confirmed by macroscopic and DSC study. The detection of phase separation using scanning electron microscopy was not successful because the blend samples were damaged by the electron beam and therefore high magnification could not be achieved. Individual PLGA and PLA implants were transparent and rod shaped after preparation by hot-melt extrusion at 80°C (Fig. 3.28), while the blends of those polymers in all ratios (PLGA:PLA, 1:2, 1:1 and 2:1) became visually turbid. The most opaque sample was the PLGA/PLA blend in the ratio of 1:1 hot-melt extrudate. For DSC, the thermogram of PLGA 502H/PLA 202H (1:1) blend extrudates revealed two distinct T_g on both the first and second DSC run (Fig. 3.29). The distinct T_g were more clearly detected from the first cycle of DSC than those from the second cycle due to the endothermic thermal history. A similar result was found with the other blend ratios (PLGA: PLA, 2:1 and 1:2) (data not shown). The observation of two polymer phases (a polymer emulsion) and two separated T_g from PLGA/PLA blends in the different ratios (2:1, 1:1 and 1:2) indicated the immiscibility of the polymer blends (Cameron et al. 2002; Roths et al. 2002; Lipatov 2006).

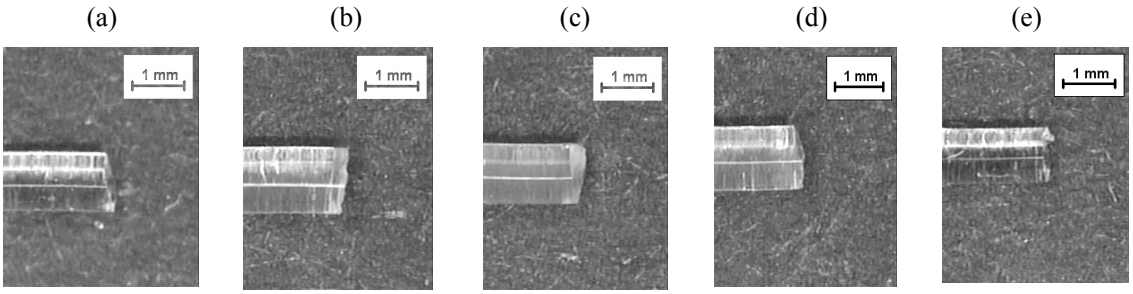


Fig. 3.28. Morphology of PLGA 502H/ PLA 202H blend implants prepared by hot-melt extrusion; PLGA: PLA ratio (a) 1:0, (b) 2:1, (c) 1:1, (d) 1:2 and (e) 0:1.

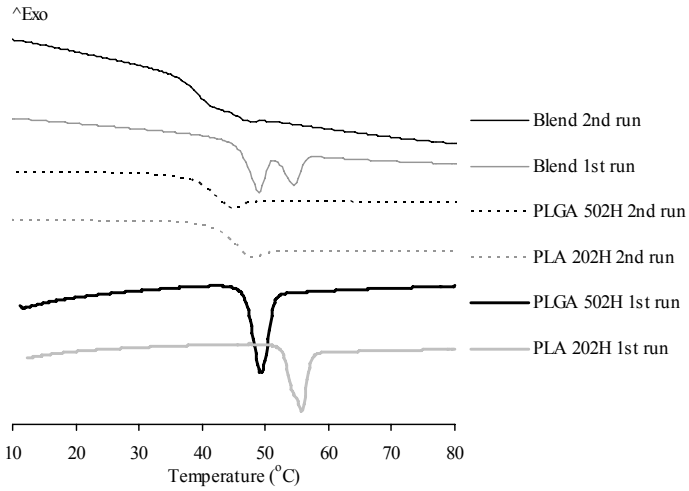


Fig. 3.29. DSC thermogram of PLGA 502H, PLA 202H and their blend (PLGA/PLA ratio, 1:1)

A triphasic release profile of tramadol HCl was obtained from the implant using only PLGA 502H (Fig. 3.30). The tramadol HCl release showed an initial burst (on the first day, 6.1%) followed by a slow release. After day 7, the release increased until complete drug release was achieved. By contrast, an initial release (of 6.5%) followed by a continuous release of tramadol HCl from the PLA implant was found (Fig. 3.30). The initial burst release from PLGA and PLA implants is caused by the releases of drug particles located at the periphery of the implants (Dorta et al. 2002; Wang et al. 2002; Aviv et al. 2007). The slower release during the second release phase was attributed to drug diffusion from the inner part of the implants. The drug had to diffuse through a longer path length resulting in a slower release in comparison with the initial release phase. During the last stage of drug release, the rate of release was increased because the polymer degradation progressed to erosion and a less dense

matrix was achieved (Wang et al. 2002). In contrast to PLGA, a continuous release from PLA implant was found after the initial burst release, and this is due to drug diffusion in the non-erosion stage of PLA.

PLGA blending with PLA had an impact on tramadol HCl releases. The releases of PLGA502H/PLA blends in different ratios changed to smooth release profiles (Fig. 3.30). The release profiles were prolonged, and became a continuous release profile with increasing PLA 202H. A linear relationship between the percentage of tramadol HCl release and time was achieved from the PLGA502H/PLA (1:2) implants. The blend ratio having the highest R^2 value (0.9922) was the PLGA502H/PLA (1:2) implants.

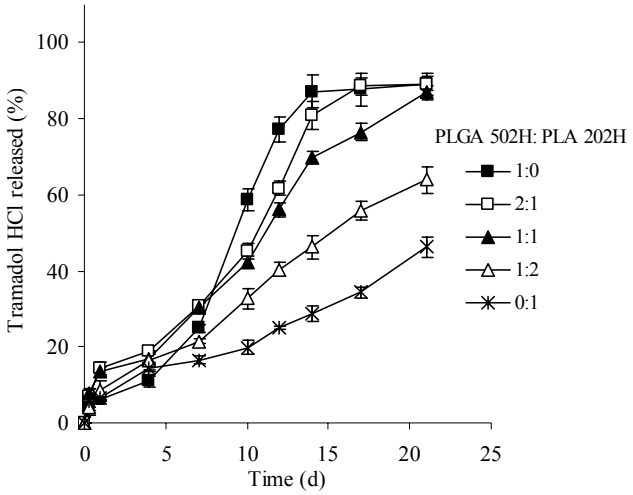


Fig. 3.30. Tramadol HCl release from PLGA 502H/ PLA 202H blend hot-melt extruded implants

The mass loss of PLGA502H was faster than that of PLA because of the more rapid polymer degradation. The PLGA 502H/PLA blend mass loss was observed to be between the PLGA and PLA profiles (Fig. 3.31). This was attributed to the immiscibility of the polymer blends. PLGA 502H degraded and eroded separately from PLA202H. The release profiles of PLGA/PLA blends were explained by these findings (relating to mass loss and immiscible blends). Firstly, the initial release was caused by the drug diffusion. When PLGA 502H degraded separately from PLA and leached into the medium, the drug release was controlled and prolonged by the remaining PLA, resulting in the continuous release profiles.

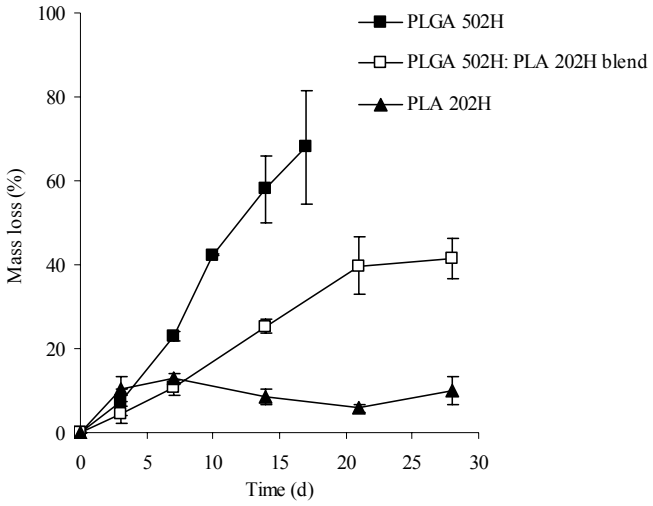


Fig. 3.31. Moss loss of PLGA 502H/ PLA 202H blend (1:1)

Tramadol HCl releases from PLGA/PLA blend implants were affected by the PLGA molecular weight represented as inherent viscosity (Fig 3.32a). In comparison with PLGA 502H/PLA (1:1) implants (Fig 3.30), a slower and longer release profile was obtained from PLGA 503H/PLA (1:1) blend implants. The release profiles from both blends were similar in pattern and mechanism (as described above for the PLGA 502H/PLA blend implants). A more retarded and prolonged release from the PLGA 503H/PLA implant was related to the water uptake and degradation time of PLGA. A lower water uptake was found for the PLGA 503H/PLA blend implant (Fig 3.32b) resulting in a slower drug release and more extended release profiles caused by the longer degradation of PLGA 503H (Pham 2004).

With the addition of 10% w/w PEG 1500, the T_g of the PLGA 502H only implants decreased from 40.7°C to 18.4°C, and from 47.6°C to 18.9°C for the PLA 202H implants. Although the decrease in the T_g of the PLGA/PLA blends could not be detected due to the immiscibility, the maximum torque value was reduced, indicating the plasticizing effect of PEG 1500 on the blends (Table 3.15). Concerning the plasticizing effect on the drug release, a decrease in the rate of release was found from PLGA/PLA (1:1) blend implants containing 10% w/w tramadol HCl (Fig. 3.33). Tramadol HCl release rates were decreased as PEG concentration increased (% w/w based on polymer). A similar effect on the drug release when PEG was used as a plasticizer was reported previously for PLA films (Tan et al. 2004). This finding

was attributed to the denser matrix formation by the presence of a plasticizer, which plays a same role as an increase in the extrusion temperature.

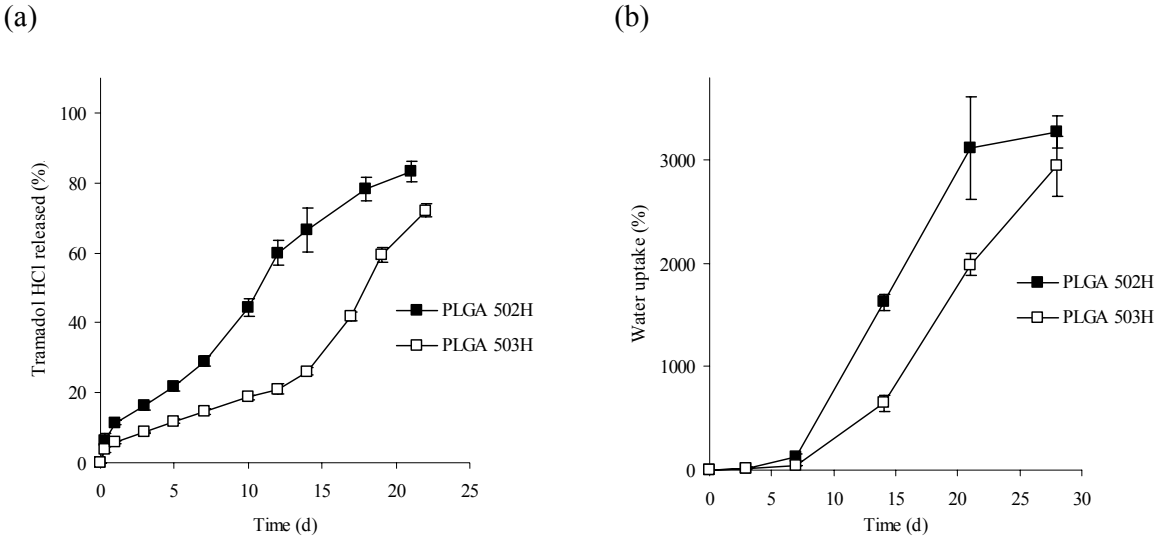


Fig. 3.32. Comparison of 10% w/w tramadol HCl releases between different inherent viscosity PLGA in the ratio of PLGA/ PLA 202H (a) 1:1 hot-melt extruded implants (b) water uptake of PLGA/ PLA 202H (1:1) hot-melt extruded implants

The releases from PLGA 502H/PLA blend implants containing 10% w/w drugs with different solubility were studied. Diazepam (solubility 225 μg/ml in phosphate buffer pH 7.4 with 0.1% SDS at 37°C) showed no drug release during an initial period, followed by a continuous release (Fig. 3.34). With higher solubility drugs (tramadol HCl, 800 mg/ml; and dexamethasone salt, 430 mg/ml in phosphate buffer pH 7.4 at room temperature), faster drug releases were observed due to the higher initial release generated by drug diffusion. With the exception of the initial phase, the profiles ran in parallel. Although, dexamethasone salt has the lower water solubility than tramadol HCl, a faster dexamethasone salt release was observed when the drug release was caused by PLGA degradation (after day 10). This was attributed to the acid-base properties of the drugs. Tramadol HCl (a basic drug with a positive charge) could from ionic interactions with the negative charge of the deprotonated carboxylic end group of PLGA, resulting in a more prolonged PLGA degradation and a slower drug release (Fig. 3.34), whereas dexamethasone salt (a basic drug) had only weak a interaction with PLGA (Miyajima et al. 1998; Klose et al. 2008).

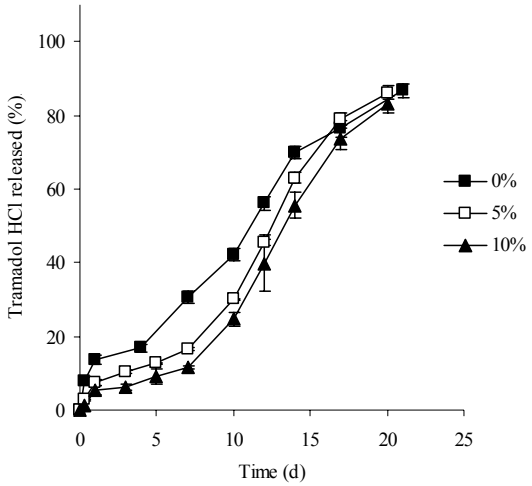


Fig. 3.33. Effect of PEG 1500 as a plasticizer on tramadol HCl release from PLGA 502H/ PLA 202H (1:1) implants

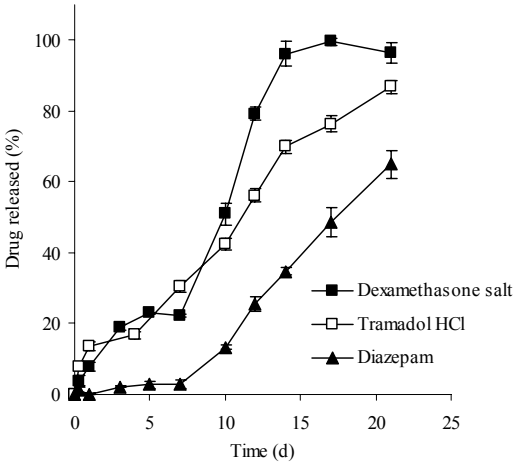


Fig. 3.34. Comparison of drug releases from PLGA 502H/ PLA 202H (1:1) blend implants containing 10% w/w drug loading

3.3.3. Conclusion

PEG acted as a plasticizer for PLGA. The melt viscosity, as represented by the maximum torques during hot-melt extrusion, decreased with an increase in PEG 1500 concentration. The addition of PEG 1500 improved the mechanical properties of PLGA hot-melt extrudates. The tensile strength was decreased and the elongation at break was increased. The crystalline PEG 1500 peak disappeared from the DSC thermogram as a result of the dissolution of PEG

1500 at 10% w/w into the PLGA hot-melt extrudates. The increase in PEG 1500 concentration was proportional to the decrease in T_g. The T_g predicted by the Gordon-Taylor equation fitted the experimental T_g data well in comparison to the prediction from the Fox equation. Upon storage, recrystallization of PEG 1500 with 15% and 20% w/w in PLGA hot-melt extrudates was observed. At lower concentrations, the hot-melt extrudates were stable during the study. Based on the recrystallization of PEG 1500, the recommended concentration of PEG 1500 as a plasticizer for PLGA should be less than 13% w/w. Although the mass loss of PLGA remains unchanged with the incorporation of PEG 1500 up to 20% w/w, the water uptake increased as a function of the PEG concentration. The drug release profiles from PLGA implants prepared by hot-melt extrusion were sigmoidal curves. The release rates were slow at the beginning of the release and increased dramatically when reaching the onset of mass loss. The drug releases form PLGA 502H were faster than those from PLGA 503H due to its shorter degradation time. The addition of PEG 1500 as a plasticizer to PLGA implants suppressed the initial burst release only for the implants containing 10% w/w tramadol HCl because of its higher water solubility compared to diazepam.

Hot-melt extrusion of PLGA/tristearin (20-40%w/w) containing 10% w/w PEG 1500 as a plasticizer was successful. After hot-melt extrusion, no change in the physical state of tristearin in the implants was observed. The blend of PLGA and tristearin was immiscible. The release profiles of diazepam from PLGA hot-melt extruded implants could be modified from the dominant degradation-controlled release to diffusion-controlled release by the addition of tristearin to the formulations. The increase in porosity of PLGA/tristearin implants and the higher K_{app} of diazepam resulted in a diffusion-controlled release mechanism, and thus continuous release profiles. For incorporation of drugs with higher water solubility and lower log partition coefficients, similar profiles with a shorter duration of drug release were obtained.

Blending PLGA/PLA was also a useful method to modify the release profiles of implants prepared by hot-melt extrusion. Melt viscosity as represented by the maximum torque was dependent on the inherent viscosity of the individual PLGA and PLA components. The blends of PLGA and PLA (PLGA/PLA ratios, 2:1, 1:1 and 1:2) were immiscible. Tramadol HCl release from pure PLGA and PLA implants showed triphasic and biphasic release

profiles, respectively. A continuous release from PLGA implants could be achieved by blending PLGA with a PLA polymer. A smooth and continuous tramadol HCl release profile from PLGA/PLA blend implants was explained by the immiscibility and mass loss of PLGA/PLA blends. The addition of PEG 1500 as a plasticizer, the change of polymer ratio, the PLGA inherent viscosity, and the drug solubility affected the drug release from PLGA/PLA hot-melt extruded implants.

The drug release from PLGA implants prepared by hot-melt extrusion could be modified by the addition of additives and polymer blends. PEG acted as a hydrophilic additive and a solid plasticizer to suppress the initial drug release due to the formation of a denser matrix. It was miscible with the polymer, whereas the addition of tristearin and the blends of PLGA/PLA were immiscible. The drug release profiles changed from the biphasic or triphasic to continuous releases.

4. Summary

The release pattern of PLGA implants depended on the drug solubility. For highly water-soluble drugs such as dexamethasone salt, a continuous release profile was achieved by the combination of curing and coating after compression to form the implants. A pulsatile release was obtained from theophylline loaded PLGA implants, a model for slightly water-soluble drugs. The initial burst release from theophylline implants was suppressed by coating and solvent dipping due to the presence of a release barrier and sealing of the pores on the surface of the implants, respectively. The lag time of the pulsatile release could be controlled by changes in the implant cores and coating materials. The replacement of the implant core by PLGA of a higher inherent viscosity led to a longer lag time as a result of a longer degradation time. The lag times could also be prolonged by a change in coating material from PLGA 502H to PLGA 503H. Using tripalmitin as a coating material resulted in a longer lag time compared to using PLGA as a coating material, and the mechanism of pulsatile release was changed from degradation of the polymer core to the rupture of tripalmitin. PLA as a coating material caused a prolonged lag time in comparison with PLGA due to its longer degradation time. The addition of $Mg(OH)_2$ into the core provided a continuous and sustained theophylline release regardless of the type of polymer coating.

Maximum torques during hot-melt extrusion were dependent on the inherent viscosity of PLGA, extrusion temperature, drug loading and drug properties, when keeping a constant screw rotation speed. The incorporation of ibuprofen into PLGA could reduce the maximum torque and T_g of PLGA caused by its plasticizing effect. A pulsatile drug release profile from PLGA hot-melt extruded implants was achieved, demonstrated by a lag time after an initial burst release, followed by a second burst or late rapid release phase. The plasticizing effect of ibuprofen on PLGA led to higher water uptake, faster mass loss, and thus the fastest drug release in comparison with the other model drugs. The initial burst release from PLGA implants prepared by hot-melt extrusion increased with an increase in drug loading, decrease in inherent viscosity of PLGA and higher water solubility of the drug. The change in processing parameters, PLGA inherent viscosity, drug solubility and the presence of coating played an important role on the lag times of pulsatile release from PLGA implants. The factors generating the acceleration of PLGA degradation led to shorter lag-times, except the drug solubility. The second burst release phase was influenced by the drug solubility and acid-base properties. The release after the lag time was slowed with higher diazepam drug loading because of its low solubility. The release of a basic drug (tramadol HCl) was

prolonged due to a possible ionic interaction. The replacement of phosphate buffer of pH 7.4 by Lipofundin to mimic in vivo subcutaneous tissue condition resulted in less water uptake, the deformation of the PLGA implant, and faster diazepam release during the diffusion phase due to the decrease in the T_g of PLGA, which is due to the presence of glycerol in the formulation.

PEG acted as a plasticizer for PLGA. The melt viscosity, as represented by the maximum torques during hot-melt extrusion, decreased with an increase in PEG 1500 concentration. The addition of PEG 1500 improved the mechanical properties of PLGA hot-melt extrudates. The tensile strength was decreased and the elongation at break was increased. The crystalline PEG 1500 peak disappeared from the DSC thermogram as a result of the dissolution of PEG 1500 at 10% w/w into the PLGA hot-melt extrudates. The increase in PEG 1500 concentration was proportional to the decrease in T_g. The T_g predicted by the Gordon-Taylor equation fitted the experimental T_g data well in comparison to the prediction from the Fox equation. Upon storage, recrystallization of PEG 1500 with 15% and 20% w/w in PLGA hot-melt extrudates was observed. At lower concentrations, the hot-melt extrudates were stable during the study. Based on the recrystallization of PEG 1500, the recommended concentration of PEG 1500 as a plasticizer for PLGA should be less than 13% w/w. Although the mass loss of PLGA remains unchanged with the incorporation of PEG 1500 up to 20% w/w, the water uptake increased as a function of the PEG concentration. The drug release profiles from PLGA implants prepared by hot-melt extrusion were sigmoidal curves. The release rates were slow at the beginning of the release and increased dramatically when reaching the onset of mass loss. The drug releases form PLGA 502H were faster than those from PLGA 503H due to its shorter degradation time. The addition of PEG 1500 as a plasticizer to PLGA implants suppressed the initial burst release only for the implants containing 10% w/w tramadol HCl because of its higher water solubility compared to diazepam.

Hot-melt extrusion of PLGA/tristearin (20-40%w/w) containing 10% w/w PEG 1500 as a plasticizer was successful. After hot-melt extrusion, no change in the physical state of tristearin in the implants was observed. The blend of PLGA and tristearin was immiscible. The release profiles of diazepam from PLGA hot-melt extruded implants could be modified from the dominant degradation-controlled release to diffusion-controlled release by the

addition of tristearin to the formulations. The increase in porosity of PLGA/tristearin implants and the higher K_{app} of diazepam resulted in a diffusion-controlled release mechanism, and thus continuous release profiles. For incorporation of drugs with higher water solubility and lower log partition coefficients, similar profiles with a shorter duration of drug release were obtained.

Blending PLGA/PLA was also a useful method to modify the release profiles of implants prepared by hot-melt extrusion. Melt viscosity as represented by the maximum torque was dependent on the inherent viscosity of the individual PLGA and PLA components. The blends of PLGA and PLA (PLGA/PLA ratios, 2:1, 1:1 and 1:2) were immiscible. Tramadol HCl release from pure PLGA and PLA implants showed triphasic and biphasic release profiles, respectively. A continuous release from PLGA implants could be achieved by blending PLGA with a PLA polymer. A smooth and continuous tramadol HCl release profile from PLGA/PLA blend implants was explained by the immiscibility and mass loss of PLGA/PLA blends. The addition of PEG 1500 as a plasticizer, the change of polymer ratio, the PLGA inherent viscosity, and the drug solubility affected the drug release from PLGA/PLA hot-melt extruded implants.

The drug release from PLGA implants prepared by hot-melt extrusion could be modified by the addition of additives and polymer blends. PEG acted as a hydrophilic additive and a solid plasticizer to suppress the initial drug release due to the formation of a denser matrix. It was miscible with the polymer, whereas the addition of tristearin and the blends of PLGA/PLA were immiscible. The drug release profiles changed from the biphasic or triphasic to continuous releases.

5. Zusammenfassung

Das Freisetzungsverhalten der PLGA-Implantate war abhängig von der Arzneistofflöslichkeit. Für Arzneistoffe mit hoher Wasserlöslichkeit wie der Salzform von Dexamethason konnte eine kontinuierliche Freigabe erreicht werden durch die Kombination von Tempern und Überziehen des Implantats nach der Verpressung. Eine pulsatile Freisetzung wurde für Theophyllin beladene Implantate erhalten, einem Modellarzneistoff mit schlechter Wasserlöslichkeit. Die hohe initiale Arzneistofffreisetzung von Theophyllin-Implantaten konnte entweder durch Überziehen des Implantats oder Eintauchen in ein Lösemittel unterdrückt werden, wobei jeweils die Anwesenheit einer Freisetzungsbarriere oder der Verschluß der oberflächlichen Poren verantwortlich gemacht werden konnten. Die Lag-Phase der pulsatilen Freisetzung konnte durch Veränderungen des Implantatkerns und des Überzugsmaterials kontrolliert werden. Der Wechsel des Kernmaterials zu PLGA mit einer höheren Viskosität führte zu einer verlängerten Lag-Phase durch Verlängerung der Abbaudauer. Eine weitere Möglichkeit zur Verlängerung der Lag-Phase war die Nutzung von PLGA 503H als Überzugsmaterial anstelle von PLGA 502H. Die Nutzung von Tripalmitin als Überzugsmaterial resultierte in längeren Lag-Phasen als die Nutzung von PLGA. Der Freisetzungsmechanismus veränderte sich von PLGA Abbau kontrolliert zu Reißen des Tripalmitinfilms. PLA verursachte längere Lag-phasen als Überzugsmaterial im Vergleich zu PLGA durch seine langsamere Abbaugeschwindigkeit. Die Zugabe von Magnesiumhydroxid zum Kern führte zu einer kontinuierlichen und verlängerten Freigabe von Theophyllin unabhängig von der Art des Überzugs.

Die maximale Drehkraft während der Heißschmelzextrusion war abhängig von der Viskosität des PLGAs, der Extrusionstemperatur, von der Wirkstoffbeladung und den Eigenschaften des verwendeten Arzneistoffes, sofern die Rotationsgeschwindigkeit der Schrauben konstant gehalten wurde. Die Einarbeitung von Ibuprofen in PLGA konnte die maximale Drehkraft und die Glasübergangstemperatur von PLGA durch seinen Weichmachereffekt reduzieren. Ein pulsatiles Wirkstoffreisetzungsprofil aus PLGA Implantaten konnte erreicht werden. Eine verzögerte Freisetzung nach einer initialen Burstfreisetzung konnte gezeigt werden, gefolgt von einem zweiten Burst oder auch einer späten rapiden Freisetzungsphase. Der Weichmachereffekt des Ibuprofens auf das PLGA führte zu einer höheren Wasseraufnahme und damit auch zu einer schnelleren Wirkstofffreisetzung sowie einem schnelleren Massenverlust verglichen mit anderen Wirkstoffen. Die initiale Freisetzung wurde gesteigert durch einer Erhöhung der Wirkstoffbeladung, Verringerung der Viskosität des PLGAs und

durch Arzneistoffe mit höherer Wasserlöslichkeit. Die Änderung der Prozessparameter, der logarithmischen PLGA Viskosität, der Wirkstofflöslichkeit und das Vorhanden sein eines Überzuges spielte eine Rolle bei der Lag-phase der pulsatilen Freisetzung der PLGA-Implantate. Alle Faktoren außer der Wirkstofflöslichkeit, die zu einer Beschleunigung des PLGA-Abbaus führten, führten zu einer Verkürzung der Lag-Phase. Die aufgetretene zweite Burst-Phase war von der Löslichkeit des Wirkstoffes und dessen Säure-Base-Eigenschaften abhängig. Die Freisetzung nach der zweiten Lag-Phase wurde durch die höhere Arzneistoffbeladung mit Diazepam wegen dessen geringer Löslichkeit verlangsamt. Die Freisetzung des basischen Wirkstoffes Tramadol-HCl wurde wahrscheinlich durch ionische Wechselwirkungen verlängert. Der Austausch des Phosphatpuffers pH 7,4 mit Lipofundin, um die in-vivo Bedingungen des subcutanen Gewebes zu imitieren, resultierte in einer verringerten Wasseraufnahme, Deformation des PLGA-Implantates und einer schnelleren Diazepamfreisetzung während der Diffusionsphase. Dies wurde begründet mit der Herabsetzung der Glasübergangstemperatur des PLGA‘s durch den Weichmachereffekt des in der Formulierung enthaltenen Glycerols.

PEG fungierte als Weichmacher für PLGA. Die Schmelzviskosität, dargestellt als maximaler Torque-Wert während der Schmelzextrusion, sinkt mit steigender PEG 1500 Konzentration. Der Zusatz von PEG 1500 verbesserte die mechanischen Eigenschaften von PLGA-Extrudaten. Die Dehnungsfestigkeit war herabgesetzt und die Bruchdehnung erhöht. Der Peak im DSC Thermogramm hervorgerufen von kristallinem PEG verschwand mit 10% m/m PEG 1500, da es sich bei diesem Gehalt in den PLGA Extrudaten auflöste. Die Erhöhung der PEG 1500 Konzentration verhielt sich proportional zur Senkung der Glasübergangstemperatur. Die vorhergesagte Glasübergangstemperatur laut Gordon-Taylor Gleichung stimmte gut mit der experimentell ermittelten Glasübergangstemperatur. Während der Lagerung konnte eine Rekristallisation von PEG 1500 in den Konzentrationen 15% und 20% m/m in den PLGA-Extrudaten beobachtet werden. Bei niedrigeren Konzentrationen waren die Extrudate während der gesamten Studie stabil. Aufgrund der Rekristallisation von PEG 1500, ist ein Zusatz von PEG 1500 als Weichmacher von weniger als 13% m/m empfehlenswert. Obwohl der Massenverlust von PLGA bei der Einarbeitung von bis zu 20% m/m PEG 1500 unverändert blieb, stieg jedoch die Wasseraufnahme mit steigender PEG Konzentration an. Das Wirkstoff-Freisetzungsprofil von PLGA-Implantaten, hergestellt mittels Schmelzextrusion, zeigte einen sigmoiden Kurvenverlauf. Die Freisetzung war zu

Beginn langsam und erhöhte sich drastisch beim Einsetzen des Massenverlustes. Die Wirkstofffreisetzung aus PLGA 502H war aufgrund der kürzeren Abbauzeit schneller als die aus PLGA 503H. Der Zusatz von PEG 1500 als Weichmacher zu PLGA-Implantaten unterdrückte die initiale Wirkstofffreisetzung nur in Implantaten mit einem Gehalt von 10% m/m Tramadol HCl aufgrund der besseren Wasserlöslichkeit im Vergleich zu Diazepam.

PLGA/Tristearin, das 10% PEG 1500 als Weichmacher enthielt konnte erfolgreich schmelzextrudiert werden. Dabei konnte keine Veränderung der physikalischen Form beobachtet werden. Das Gemisch aus PLGA und Tristearin war nicht mischbar. Durch die Zugabe von Tristearin zur Formulierung konnte das Freisetzungsverhalten von Diazepam aus PLGA-Implantaten von vorrangig PLGA Abbau kontrollierter Freisetzung zu Diffusionskontrollierter Freisetzung mit kontinuierlichem Profil verändert werden. Dies wurde verursacht durch eine erhöhte Porosität der PLGA/Tristearin Implantate und einem höheren Verteilungskoeffizienten von Diazepam. Ähnliche Profile mit kürzerer Freisetzungsdauer wurden für Arzneistoffe mit höherer Löslichkeit und niedrigerem Verteilungskoeffizienten erhalten.

Das Freisetzungsprofil von durch Schmelzextrusion hergestellten Implantaten konnte durch das Mischen von PLGA und PLA modifiziert werden. Die Schmelzviskosität, repräsentiert durch das maximale Drehmoment, war von der inhärenten Viskosität von PLGA und PLA abhängig. Die Mischungen von PLGA und PLA (PLGA/PLA Verhältnis 2:1, 1:1 und 1:2) waren nicht miteinander mischbar.

Das Freisetzungsverhalten von Tramadol aus PLGA oder PLA Implantaten war bi- beziehungsweise triphasisch . Ein kontinuierliches Freisetzungsverhalten konnte durch das Mischen von PLGA mit PLA erreicht werden, was durch die Unmischbarkeit und dem Grad des Massenverlustes der Mischungen erklärt werden konnte. Die Beimischung von PEG 1500 als Weichmacher, die Veränderung des Verhältnisses von PLGA zu PLA, die inhärente Viskosität von PLGA und die Arzneistofflöslichkeit beeinflussten die Arzneistofffreisetzung von durch Schmelzextrusion hergestellten Implantaten.

Die Arzneistofffreisetzung aus mittels Schmelzextrusion hergestellten PLGA-Implantaten konnte durch die Zugabe von Additiven sowie durch die Verwendung von

Polymergemischen gesteuert werden. PEG, als hydrophiler Zusatzstoff, und als Feststoff zugesetzte Weichmacher unterdrückten die initiale Arzneistofffreigabe durch Bildung einer dichteren Matrix und waren allgemein mischbar. Hingegen waren Tristearin und PLA nicht mit PLGA mischbar. Die Freisetzungsprofile gingen von bi- oder triphasischen Verläufen in kontinuierliche über.

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7. Publications and Presentations

Publications

Shuwisitkul, D. and R. Bodmeier. Pulsatile release pattern from PLGA implants prepared by direct compression. (in preparation)

Shuwisitkul, D. and R. Bodmeier. Pulsatile release pattern from PLGA hot-meltextruded implants: Influence of processing parameters, drug properties and in vivo simulation. (in preparation)

Shuwisitkul, D. and R. Bodmeier. Influence of additives on mechanism of drug release profiles from PLGA implants (in preparation)

Presentations

Shuwisitkul, D. and R. Bodmeier. Preparation of poly(lactide-co-glycolide) implants by hot-melt extrusion. AAPS, San Antonio, Texas, USA, 2006.

Shuwisitkul, D. and R. Bodmeier. Modified release patterns of PLGA hot-melt extruded implants. CRS, Long beach, California, USA, 2007.

Shuwisitkul, D. and R. Bodmeier. Pulsatile release from biodegradable hot-melt extruded implants. AAPS, San Diego California, USA, 2007.

Shuwisitkul, D. and R. Bodmeier. Development of PLGA/PLA polymer blend hot-melt extruded implants. 6th World meeting, Barcelona, Spain, 2008.

8. Curriculum Vitae

Curriculum Vitae

For reasons of data protection,
the curriculum vitae is not included in the online version