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Review

The mechanisms of drug release in poly(lactic-co-glycolic acid)-based drug delivery systems—A review

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ABSTRACT

Poly(D,L-lactic-co-glycolic acid) (PLGA) is the most frequently used biodegradable polymer in the controlled release of encapsulated drugs. Understanding the release mechanisms, as well as which factors that affect drug release, is important in order to be able to modify drug release. Drug release from PLGA-based drug delivery systems is however complex. This review focuses on release mechanisms, and provides a survey and analysis of the processes determining the release rate, which may be helpful in elucidating this complex picture. The term release mechanism and the various techniques that have been used to study release mechanisms are discussed. The physico-chemical processes that influence the rate of drug release and the various mechanisms of drug release that have been reported in the literature are analyzed in this review, and practical examples are given. The complexity of drug release from PLGA-based drug delivery systems can make the generalization of results and predictions of drug release difficult. However, this complexity also provides many possible ways of solving problems and modifying drug release. Basic, generally applicable and mechanistic research provides pieces of the puzzle, which is useful in the development of controlled-release pharmaceuticals.

Contents

1. Introduction

Poly(D,L-lactic-co-glycolic acid) (PLGA) has been used in various areas, such as the controlled release of encapsulated drugs, tissue engineering (Oh and Lee, 2007; Wang et al., 2010), healing of bone defects (Bertoldi et al., 2008), and in vaccines (Feng et al., 2006; Jiang et al., 2005). Several PLGA-based products for the controlled release of encapsulated proteins or peptides are on the market. The use of biopharmaceuticals, such as proteins and peptides, and of hydrophobic drugs with low oral bioavailability, is growing (Närhi and Nordström, 2005; Pisal et al., 2010; Wiscke and Schwendeman, 2008). As the oral bioavailability of both these

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groups of pharmaceuticals is low, patient compliance is also low due to the necessity of administration by injection. The frequency of injections can be decreased by the use of controlled-release encapsulated drugs, which is very beneficial for patients who require daily and/or long-term treatment.

The reasons for the widespread use of PLGA are its biodegradability, its biocompatibility, and the fact that drug products containing PLGA have been approved for parenteral use by regulatory authorities around the world. The disadvantage associated with PLGA is the production of acids upon degradation, as is the case of many other biodegradable polymers. Several techniques for the stabilization of acid-sensitive drugs have been investigated, and this continues to be an area of intense research (Bilati et al., 2005; Houchin and Topp, 2008; Zhu and Schwendeman, 2000). Further advantages of PLGAs are that they are commercially available with very different physico-chemical properties, and that the drug release profile can be tailored by selecting PLGAs with the appropriate properties, for example, molecular weight (M_w) and the lactide:glycolide ratio (L:G) (Tracy et al., 1999; Ravivarapu et al., 2000; Zolnik and Burgess, 2008). The duration of drug release can be varied from hours (Ratajczak-Emselme et al., 2009) to several months (D'Souza et al., 2004; Lagarce et al., 2005). Furthermore, pulsed drug release is also possible (Dorta et al., 2002). Blending or co-polymerizing PLGA with other materials, or encapsulating PLGA microparticles in gels, further extends the possibility of controlling drug release (Cho et al., 2001; Galeska et al., 2005; Mundargi et al., 2008; Vila et al., 2004).

Numerous active pharmaceutical ingredients have been encapsulated in PLGA-based drug delivery systems (DDSs) with proven therapeutic effect *in vivo*, or have been released in concentrations considered sufficient for therapeutic effect, for example, siRNA (Murata et al., 2008), proteins (Gu et al., 2007), peptides (D'Souza et al., 2004), anti-cancer drugs (Mo and Lim, 2005), analgesics (Yen et al., 2001), antibiotics (Patel et al., 2008), and vaccines (Cui et al., 2007). Among the different forms of PLGA-based DDSs, microspheres or microparticles are the most common. Other types include nanoparticles (Sharma et al., 2007), films (Klose et al., 2008), cylinders (Desai et al., 2010), *in situ* forming implants or microparticles (Dong et al., 2006), scaffolds (Xiong et al., 2009), and foams (Ong et al., 2009). PLGA implants may be surgically inserted at the desired location, giving the advantage of local drug delivery of, for example, antibiotics or anti-cancer drugs (Weinberg et al., 2008; Xu and Czernuszka, 2008). Nanoparticles of PLGA can also be injected intravenously, and target delivery can be obtained by conjugating an antibody or another molecule with an affinity for a specific target onto the surfaces (Chittasupho et al., 2009), for example, tumor targeting (Patil et al., 2009). Active cellular uptake of nanoparticles is possible, enabling intracellular drug delivery (Cartiera et al., 2009; Hirota et al., 2007), which is an advantage in gene delivery (Cun et al., 2010).

Knowledge of the release mechanisms and the physico-chemical processes that influence the release rate is vital in order to develop controlled-release DDSs. The two main release mechanisms associated with drug release from PLGA-based DDSs are diffusion and degradation/erosion. The release rate is often said to be diffusion-controlled initially and degradation/erosion-controlled during the final stage of the release period (D'Souza et al., 2005; Mollo and Corrigan, 2003). However, many processes or events influence the rate of drug diffusion and the degradation kinetics, for example, polymer–drug interactions (Blanco and Alonso, 1997), drug–drug interactions (Kang et al., 2008), water absorption (Desai et al., 2010), and pore closure (Kang and Schwendeman, 2007). Knowledge regarding these more detailed processes is necessary if we are to understand drug release in detail and be able to control the release rate. Drug release is often preceded by a chain of processes (e.g. water absorption, hydrolysis, and erosion). These processes are influenced by many different factors. This increases the complexity of drug release, as discussed in Section 3. The term "release mechanism" is used in different ways in the literature, which further complicates the picture. Various techniques have been used to study release mechanisms, and the results regarding release mechanisms differ, which is not surprising considering the complexity of drug release from PLGA-based DDSs. Although PLGA has received much attention as a drug carrier over the past 20 years, new insights into processes that govern drug release and new ways of modifying drug release are still being presented.

This review focuses on the mechanisms of drug release from PLGA-based DDSs, and is complementary to previous reviews that have emphasized which factors that effect drug release from mainly poly(lactic acid) (PLA)-based DDSs (Alexis, 2005), the encapsulation and release of hydrophobic drugs (Wiscke and Schwendeman, 2008), and the encapsulation and release of macromolecular drugs in PLGA and its derivates (Mundargi et al., 2008). It is also complementary to previous reviews covering other polymers in addition to PLGA, and focusing on mathematical modeling of drug release (Siepmann and Göpferich, 2001; Siepmann and Siepmann, 2008). Understanding the release mechanisms is key to developing formulations, and we believe that a deep review focusing solely on release mechanisms will make an important contribution, and help clarify the complex picture of drug release from PLGA-based DDSs. This review covers the definition of the term "release mechanism", the release mechanisms that have been reported, different techniques used for the study of release mechanisms, and the physico-chemical processes influencing drug release.

2. Definition of the term "release mechanism"

The term "release mechanism" has been defined in slightly different ways. It has been used as a description of the *way* in which drug molecules are transported or released (Kranz et al., 2000; Sansdrap and Moës, 1997), and as a description of the process or event that determines the release *rate*. Table 1 lists different release mechanisms or processes that have been reported to be the rate-controlling process in drug release. These will be further discussed in Section 5.

There are only three possible ways for drug molecules to be released from a PLGA-based DDS: (i) transport through water-filled pores, (ii) transport through the polymer, and (iii) due to dissolution of the encapsulating polymer (which does not require drug transport). Transport through water-filled pores are the most common way of release, as the encapsulated drug is usually a biopharmaceutical, such as a protein or a peptide, which are too large and too

Table 1
Processes that have been reported as release mechanisms or rate-controlling processes in drug release.

Mechanism or process	Reference
Dissolution of the drug (in combination with diffusion)	Wong et al. (2001)
Diffusion through water-filled pores	Kim et al. (2006)
Diffusion through the polymer matrix	Sun et al. (2008)
Hydrolysis	Bishara and Domb (2005)
Erosion	Shah et al. (1992)
Osmotic pumping	Jonnalagadda and Robinson (2000)
Water absorption/Swelling	Mochizuki et al. (2008)
Polymer–drug interactions	Gaspar et al. (1998)
Drug–drug interactions	Zhu and Schwendeman (2000)
Polymer relaxation	Gagliardi et al. (2010)
Pore closure	Kang and Schwendeman (2007)
Heterogeneous degradation	Park (1995)
Formation of cracks or deformation	Matsumoto et al. (2006)
Collapse of the polymer structure	Friess and Schlapp (2002)

hydrophilic to be transported through the polymer phase. The most common way of transport through water-filled pores is diffusion, i.e. random movements of the molecules driven by the chemical potential gradient, which can often be approximated by the concentration gradient. The other way of transport through water-filled pores is convection, which is driven by a force such as osmotic pressure (Cussler, 1997). Osmotic pressure may be created by the influx of water into a non-swelling system. Drug transport driven by this force is called osmotic pumping (Hjärtstam, 1998), and is more common in drug delivery systems utilizing other polymers such as ethyl cellulose (Marucci, 2009). PLGAs that absorb a large amount of water also have mobile polymer chains, and are prone to swell. As the volume of water inside increases, any significant increase in pressure will probably be compensated for by swelling and rearrangement of the polymer chains. Transport through the polymer phase may occur when the drug is small and hydrophobic (Raman et al., 2005). However, the drug must enter the water phase, either at the surface or in the pores inside the DDS, before being released. The encapsulated drug may also be released without any transport due to dissolution of the polymer, i.e. erosion. Erosion also creates pores, thus increasing the rate of diffusion. However, there is a difference between erosion leading to drug release without drug transport, and erosion that increases the rate of drug transport. The latter has been reported as a release mechanism countless times, at least after a lag period, which is often described as diffusion-controlled release (Alexis et al., 2004; Cohen et al., 1991; Goraltchouk et al., 2006; Johnson et al., 1997; Lam et al., 2000; Wang et al., 2004a; Westedt et al., 2006).

The three basic ways of drug release mentioned above, with two types of transport included in the transport through water-filled pores, result in four possible release mechanisms, if the term "release mechanism" is defined as the *way* in which the drug is released:

- diffusion through water-filled pores,
- diffusion through the polymer,
- osmotic pumping, and
- erosion (i.e. no drug transport).

These release mechanisms will be further discussed in Section 5.

However, the most common use of the term release mechanism is in referring to the process that determines the *rate* of release, for example swelling, drug dissolution or polymer–drug interactions. As mentioned above, erosion can be included in both definitions, but with different meanings. Describing the process controlling the release rate is more informative than describing the way of drug release, when it comes to how drug release can be modified. Describing these processes is thus important. However, using these processes as release mechanisms leads to problems: (i) due to the complexity of the system it is not always clear which of the processes is dominating, and (ii) in a chain of processes that leads to drug release it is not obvious which one is the rate-determining process. For example, the drug may be released by diffusion through water-filled pores, and the rate of pore formation may be the rate-controlling process. Polymer erosion, which is determined by the rate of hydrolysis, *probably* determines the rate of pore formation, although the absorption of water also results in pores. Should the release mechanism be described as "pore formation", "erosion" or "hydrolysis"? And should water absorption be mentioned? How far along the chain of processes should one search for the process mainly responsible for drug release? This is probably one reason why so many different processes have been reported as the release mechanism (Table 1), which does not help clarifying the complex picture of drug release (see Section 3).

In this review, the processes defining the *way* in which the drug is released will be called the *true release mechanisms*, and the processes that control the release *rate* will be called *rate-controlling release mechanisms*. The true release mechanisms are illustrated in Fig. 1. In discussions regarding release mechanisms, it is thus recommended to first establish the true release mechanism(s), and then to discuss the rate-controlling release mechanisms in more detail. For example, bovine serum albumin (BSA) was released by diffusion through water-filled pores. The rate of diffusion depended on the degree of polymer erosion, and was slowed down by the adsorption of BSA to the polymer. In this example, the true release mechanism is diffusion through water-filled pores, and polymer erosion and polymer–drug interactions are the rate-controlling release mechanisms. BSA is released by diffusion through water-filled pores during the whole release period no matter if the degradation kinetics, the initial porosity or any other factor determines the release rate, which is the reason why the true and rate-controlling release mechanisms should be discussed separately. Knowing the true release mechanism is useful when trying to identify the rate-controlling release mechanism.

The true and rate-controlling release mechanisms could be compared to the established terms regarding mechanisms of diffusion, namely intrinsic and apparent diffusion (Macarini et al., 2010). Intrinsic is the true mechanism for diffusion, or pure diffusion. The apparent diffusion is the diffusion that can be measured and may depend on other phenomena, such as interaction between the diffusing solute and other materials. There are differences between these couples of terms, through. While diffusion through a porous network, causing an effective diffusion, would fall under the term apparent diffusion, diffusion through a porous network is the *way* in which an encapsulated drug is released and is thus a true release mechanism.

3. Factors that influence drug release from PLGA-based DDSs

3.1. Physico-chemical processes occurring in PLGA-based DDSs

Water is absorbed by the polymer immediately upon immersion in water or administration *in vivo* (Fig. 2). The rate of water absorption, or hydration, of the DDS is rapid compared to drug

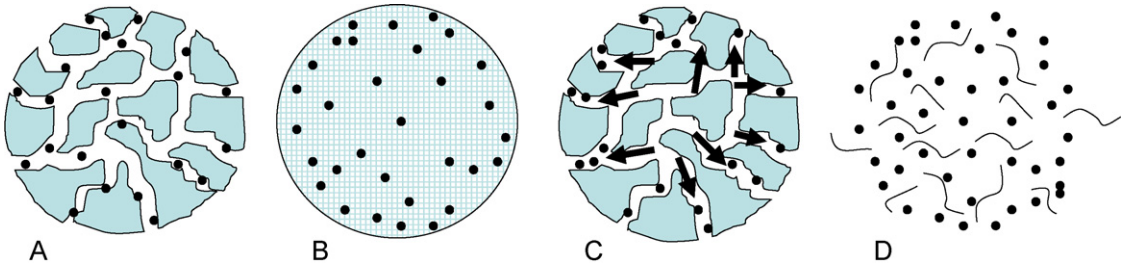


Fig. 1. True release mechanisms: (A) diffusion through water-filled pores, (B) diffusion through the polymer, (C) osmotic pumping and (D) erosion.

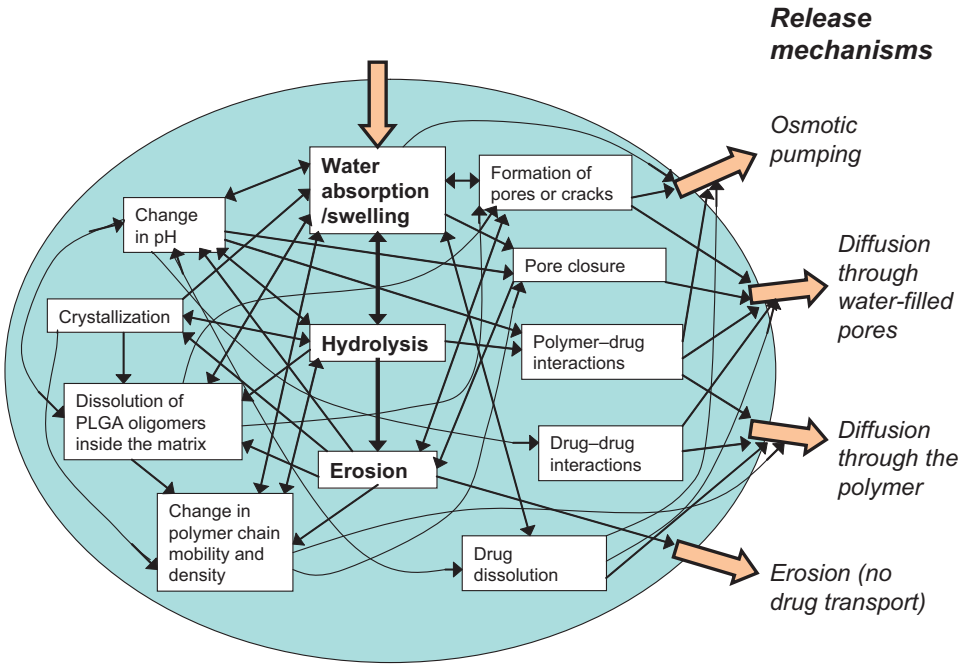


Fig. 2. The complex picture of physico-chemical processes taking place within PLGA matrices, leading to drug release. The influence of processes on drug release and on other processes is illustrated by arrows. Note that some arrows point in both directions.

release (Batycky et al., 1997; Blasi et al., 2005). Any volume occupied by water inside the polymer matrix can be regarded as a pore, and water absorption is therefore a pore-forming process. These pores are too small for drug transport during the early stage of this process, but as the number and size of water-filled pores in the polymer increase, a porous connected network allowing drug release is formed (Mochizuki et al., 2008; Webber et al., 1998).

Hydrolysis, i.e. the scission of ester bonds and subsequent decrease in M_w, starts immediately upon contact with water. Hydrolysis creates acids, which catalyzes hydrolysis (Shenderova et al., 1999). This auto-catalytic phenomenon is known to cause heterogeneous degradation inside PLGA matrices (Li and McCarthy, 1999), i.e. faster degradation at the center of the PLGA matrix than at the surface. This effect becomes more pronounced with increasing dimensions of a DDS (Dunne et al., 2000) as the acid gradient increases, but heterogeneous degradation has also been reported in particles and films with dimensions as small as 10 μm (Lu et al., 1999; Park, 1995). The polymer becomes less hydrophobic with decreasing M_w, and at 1100 Da the oligomers become water soluble (Park, 1994).

Erosion, i.e. mass loss of the polymer, starts when the dissolved polymer degradation products are able to diffuse into the release medium. PLGA normally undergoes bulk erosion, in contrast to surface erosion, as PLGA is relatively rapidly hydrated (Chen and Ooi, 2006). Dissolution of polymer degradation products and erosion create pores. Small pores, formed by water absorption or polymer erosion, grow as contact with water leads to hydrolysis, and the locally produced acids catalyze degradation and causes polymer dissolution inside the pores, leading to subsequent erosion. Small pores consequently grow, and eventually coalesce with neighboring pores to form fewer, larger pores (Batycky et al., 1997). Pores may also be closed (Fredenberg et al., 2011; Kang and Schwendeman, 2007). This phenomenon is related to the mobility of the polymer chains, and their ability to rearrange (Yamaguchi et al., 2002), which is further discussed in Section 5. The mobility of polymer chains depends on the glass transition temperature (T_g). The transport resistance is higher for PLGAs in the vitreous state, and water absorption and hydrolysis proceed more slowly. The glass transition temperature decreases with decreasing M_w (Zolnik et al., 2006).

The dissolved polymer degradation products affect the system in several ways.

(i) They are acids and thus catalyze hydrolysis.
(ii) They plasticize the polymer, which increases the rate of water absorption and decreases the transport resistance of the polymer (Mauduit et al., 1993).
(iii) They increase the osmolality inside the polymer matrix, and thus the force for water absorption.
(iv) They are known to be able to crystallize, especially if there are many repeating units of the same monomer in a row, i.e. glycolic, L-lactic or D-lactic monomers (Scckliecker et al., 2003; Vert et al., 1991). This crystallization inhibits water absorption, further degradation and transport (Li, 1999).

These dissolved degradation products are released at polymer erosion, which means that their effect on the system ceases upon erosion. The onset of rapid erosion often coincides with a cessation of the decrease in the average M_w and T_g, as the low-M_w fraction of polymer chains is released, and the effects of dissolved degradation products are lost (Yoshioka et al., 2008). The transport resistance is thus important, not only for the release of the encapsulated drug, but also for the polymer degradation kinetics. Two important processes that influence the transport resistance are pore formation and pore closure. Other processes that influence the rate of drug transport are drug dissolution, polymer–drug interactions and drug–drug interactions.

3.2. Factors influencing the physico-chemical behavior of PLGA

The processes described in Section 3.1 are affected by the properties of the DDS and the surrounding environment, which are listed in Table 2. How these affect the processes are illustrated in Fig. 3.

One method of controlling drug release is to select PLGAs with the appropriate properties. The molecular weights of PLGAs used

Table 2
Properties of the DDS and the surrounding environment that influence drug release.

The polymer	*In vitro* conditions
Molecular weight	Temperature
L:G ratio	Stirring
End-group capping	Composition of the release medium
Semi-crystallinity	pH
	Osmolality
Encapsulated substances	*In vivo* conditions
The characteristics of the drug	Sink conditions
Drug load and location	Enzymes
The characteristics of additives, such as salts, surfactants and plasticizing agents	Lipids
	Immune responses
The DDS	
Size	
Porosity	
Density	
Shape	

for controlled release are usually relatively low, often less than 50 kDa and very seldom above 150 kDa. PLGAs with molecular weights less than 10 kDa are sometimes used. The L:G ratio ranges from 50:50 to 100:0. PLA can be regarded as a 100:0 PLGA and will be included in the discussions regarding PLGA in this review. The polymer end groups may or may not be capped with a hydrophobic ester group, for example, a stearyl group (Johansen et al., 2000). Low M_w, low L:G ratio and un-capped polymer end groups result in a less hydrophobic polymer with increased rates of water absorption, hydrolysis and erosion (Husmann et al., 2002; Lu et al., 1999; Tracy et al., 1999; Zilberman and Grinber, 2008). The amount of water absorbed and the duration of drug release is highly dependent on these properties (Alexis et al., 2006; Kim et al., 2005), and the choice of PLGAs is perhaps the most important tool in drug release modification. The initial T_g is also dependent on these properties. Polymers with only the L-lactic acid may be semi-crystalline (Alexis et al., 2006). When discussing drug release from PLGA-based DDSs it is important to remember that PLGAs with different molecular weights, L:G ratios and end-group capping behave very differently. It is also important to bear in mind the dynamic nature of PLGA, as its properties and behavior change with degradation. Hydrophobic, high-M_w and slow-degrading PLGAs will eventually become more hydrophilic, low-M_w and fast-degrading PLGAs.

The encapsulated drug and additives may affect many of the processes listed above. Salts consisting of a divalent cation and a basic anion are common protein stabilizers (Takada et al., 2003; Zhong et al., 2007). Basic anions neutralize acids (Li and Schwendeman, 2005), and divalent cations can be used to stabilize proteins by complex binding, or by inhibiting acylation (Johnson et al., 1996; Sophocleous et al., 2009). Divalent cations may also be pore forming, as they probably catalyze hydrolysis (Fredenberg et al., 2007, 2009). Other common additives are plasticizing or surface active substances. The encapsulated drug or the co-encapsulated additives may affect drug release in several ways:

(i) enhanced or inhibited water absorption and hydrolysis due to increased hydrophilicity/hydrophobicity, osmolality, or due to surface active substances (Chung et al., 2006; Kang and Schwendeman, 2002),
(ii) increased or decreased rate of hydrolysis due to acid or base catalysis, or acid neutralization (Wang et al., 2004a; Zhang et al., 1997),
(iii) plasticization of the polymer (Blasi et al., 2007; Kranz et al., 2000), or
(iv) constitution of crystalline parts of the DDS.

The amount of drug encapsulated, i.e. the load, may be important as the space left vacant after drug release will probably constitute pores, facilitating further drug release (Perugini et al., 2001). The release profile may also be affected by the location of the drug inside the DDS (Berkland et al., 2003). The location of the drug may be affected by the physico-chemical properties of the drug (Sandor et al., 2001).

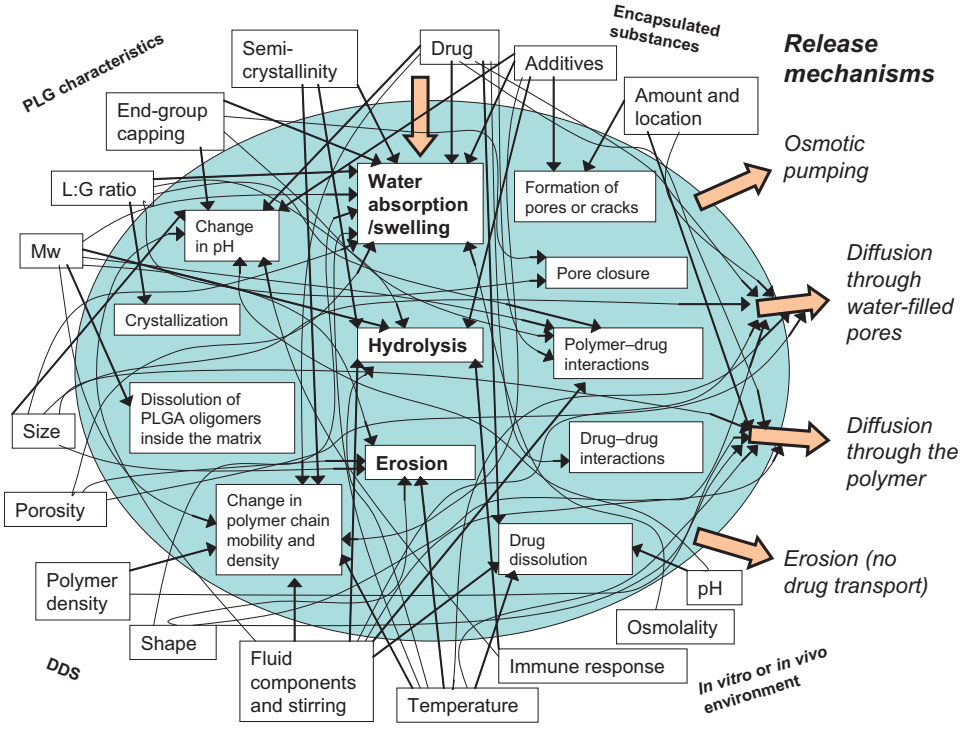


Fig. 3. The complex picture of the different factors that influence drug release from PLGA matrices. The effects of the properties of the DDS and the surrounding environment on the processes that, in turn, influence drug release are illustrated by arrows.

The characteristics of the DDS, such as the porosity and the polymer chain density, are important (Duvvuri et al., 2006; Kim and Park, 2004; Ricci et al., 2005). Large DDSs result in an increased pH gradient, and the auto-catalytic effect on degradation is enhanced (Fu et al., 2000). The shape of the DDS, in particular the ratio of surface area to volume, affects the release of the drug and the PLGA degradation products. The size of particles may effect the drug distribution within the particles (Berkland et al., 2003). Most of the properties characterizing the DDS are influenced by the manufacturing method (Yushu and Venkatraman, 2006).

The local environmental conditions also affect the processes and drug release. Increased temperature increases all chemical reactions, but also increases the mobility of the polymer and, thus, possibly the rate of pore closure. An unstirred surface layer surrounding the DDS inhibits drug release. Salts, plasticizing agents and surfactants in the release medium may affect the processes in the same way as if they were encapsulated, but with the exception that high osmolality in the release medium would decrease the rate of water absorption by the DDS (Faisant et al., 2006; Li, 1999; Okada, 1997). The pH or buffering capacity is important for the rate of degradation (Park et al., 1995), but also for the rate of pore formation and pore closure, as will be discussed in Section 5.2. The conditions must therefore be considered when designing an *in vitro* release method. Faster polymer degradation and drug release, and a shorter drug release lag-phase, have been reported *in vivo* (Spenlehauer et al., 1989; Zolnik and Burgess, 2008), and have been attributed to the effects of enzymes, lipids, non-sink conditions, possible merging of microparticles and immune responses (Grayson et al., 2004; Pratt et al., 1993; Zeng et al., 2005). The collection of macrophages around the DDS is an immune response, and the phagocytosis of small microparticles, and the release of acidic products by these cells may increase the rate of degradation (Anderson and Shive, 1997). The formation of a fibrous capsule around injected particles, which may decrease the pH due to acidic degradation products, has also been reported (Sastre et al., 2007).

4. Studies of release mechanisms

4.1. The shape of the release profile

The release profile is sometimes used as the basis for mechanistic evaluation. Although zero-order release is the most commonly preferred profile, mono-phasic release from PLGA-based DDSs is rare. Drug release is sometimes bi-phasic, but a tri-phasic profile is probably most common. Large particles or DDSs often exhibit this tri-phasic release profile due to heterogeneous degradation (Berchane et al., 2007; Berkland et al., 2003). Small particles and particles coated with a thin PLGA film often exhibit a bi-phasic release profile with a relatively rapid second phase (Fredenberg, 2011; Sansdrap and Moës, 1997). Combining particles of different sizes has been shown to offer a means of altering the drug release profile, from a Fickian diffusion profile and a sigmoidal profile to a zero-order profile (Berkland et al., 2002).

Phase I in the classic tri-phasic release profile is usually described as a burst release, and has been attributed to non-encapsulated drug particles on the surface or drug molecules close to the surface easy accessible by hydration (Wang et al., 2002). Other reasons for burst release may be the formation of cracks and the disintegration of particles (Huang and Brazel, 2001). Phase II is often a slow release phase, during which the drug diffuses slowly, either through the relatively dense polymer or through the few existing pores, while polymer degradation and hydration proceed. Phase III is usually a period of faster release, often attributed to the onset of erosion. This phase is sometimes called the *second burst*. However, all release profiles do not follow the traditional tri-phasic release profile. If the second phase is rapid, there may be a slower phase at the end of the release period (Bae et al., 2009; Han et al., 2010). The release profile may not exhibit any burst release (Pan et al., 2006). Some examples of different release profiles are given in Fig. 4, while Table 3 summarizes some of the explanations of the different release profiles. The term *degradation* is used with slightly different meanings in different studies: i.e. both hydrolysis and erosion of the polymer, or the combination of the two processes. In this paper, except in Table 3, *degradation* refers to the M_w-decreasing process of hydrolysis, which is the most common use of the term.

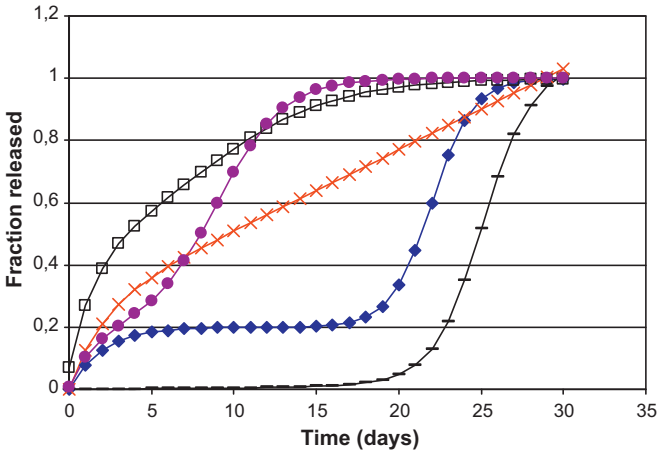


Fig. 4. Release profiles consisting of different phases. Open squares: burst and a rapid phase II. Filled circles: tri-phasic release with a short phase II. Crosses: burst and zero-order release. Filled diamonds: tri-phasic release. Dashes: bi-phasic release, similar to tri-phasic but without the burst release.

There are many possible explanations of the different phases, as can be seen in Table 3. The complexity of the processes or events that enhance or inhibit drug release (illustrated in Fig. 2) makes it difficult to draw any conclusions merely from the release profile. A slow second phase, or lag-phase, may not necessarily be caused by a dense polymer with low porosity, which is the common explanation. It may also be caused by pore closure, polymer–drug interactions or drug–drug interactions that inhibit the release of the drug (Blanco and Alonso, 1997; Kang et al., 2008; Kang and Schwendeman, 2007). In a study on the release of leuprolide acetate from PLGA microparticles, the interior became porous while the surface remained non-porous at an early stage of the slow second phase of a tri-phasic release pattern. It is logical to assume that diffusion inside the particle was rapid and that the low porosity at the surface was the reason for the slow release. Adding medium chain triglycerides to the microparticles made the surface porous, in addition to increasing the porosity inside, and the slow second phase disappeared (Luan and Bodmeier, 2006). The second burst, or rapid phase III, is commonly attributed to the onset of polymer erosion. However, it may also be caused by cracks or the disintegration of particles (Matsumoto et al., 2006). As the pH and other microenvironmental characteristics change with time, the conditions causing the slow release may have been altered, for example, such that the process of pore formation dominates over pore closure. Friess and Schlapp (2002) found that the rapid release phase could be phase II or III depending on the type of PLGA. The onset of rapid drug release was found to be correlated with massive swelling, erosion and deformation of the microparticles, and the increase in release rate was ascribed to the accessibility of new surfaces. One problem with visual analysis of the release profile is that the start and end-point of each phase is not always obvious. Phases may also have their origin in superimposing processes or events that counteract each other. Attributing a second burst release to pore formation caused by degradation/erosion is probably often accurate, however, cau-

Table 3
Explanations of the origins of the phases observed during drug release.

Phase I	Phase II	Phase III	Reference
Burst	Slow diffusion-controlled release	Rapid erosion-controlled release	Loo et al. (2010)
No burst	Slow diffusion-controlled release	On-set of degradation. Erosion-controlled release	Alexis et al. (2004)
Diffusion-controlled release of drug molecules at the surface or in pores initially connected to the surface	Dependent on diffusion and erosion	Dependent on diffusion and erosion	Zolnik et al. (2006)
Similar to the row above	Lag-phase, as the first and second phase did not overlap	Second phase, erosion-controlled	Johnson et al. (1997)
Similar to the row above	Slow and minimal release	Rapid release. Rapid water absorption associated with sudden mass loss	Duvvuri et al. (2006)
Similar to the row above	Degradation and erosion.		Capan et al. (2003)
Burst. Drug molecules on or with access to the surface	Slow diffusion-controlled release	Onset of bulk degradation	Chen and Ooi (2006)
Burst	Diffusion governed by water absorption and swelling	Erosion phase at which degradation occurs	Xu and Czernuszka (2008)
Burst	Diffusion due to hydration	Faster diffusion due to erosion. The onset of this phase depends on the rate of hydration	D'Souza et al. (2005)
Burst. Surface-bound and poorly encapsulated drugs may diffuse through pores and cracks	Slow diffusion, which may be attributed to binding of the drug to the polymer	Faster diffusion through the eroding matrix. Decrease in polymer M_w increases the gaps in the matrix	Janoria and Mitra (2007)
Burst. Solvent penetration and glass transition	Limited drug dissolution. Polymer degradation and relaxation	Diffusion through water-filled pores	Lao et al. (2008)

tion should be exercised when drawing conclusions merely from the release profile.

4.2. Mathematical modeling

A variety of mathematical models have been used to describe drug release from PLGA-based DDSs. Mathematical models can be divided into two categories: empirical/semi-empirical models and mechanistic mathematical models (Siepmann and Siepmann, 2008). Empirical/semi-empirical models are purely mathematical descriptions, and are not based on any real chemical, physical of biological phenomenon. These do not provide any insight into which factors that control drug release, and their predictive power is low. However, they may still be useful, for example, in describing different phases of the drug release, which can be helpful in product development (Duvvuri et al., 2006). Mechanistic mathematical models, on the other hand are based on real phenomena, such as diffusion, degradation and erosion, and are useful tools in the mechanistic understanding of the release process. The values of some parameters may be determined in complementary experiments, or fitted using experimental data. Several parameters may be fitted simultaneously. The validity of a model increases if its predictions are in good agreement with independent experimental data. Predictability has been demonstrated for some models (Faisant et al., 2003; Guse et al., 2006a; Raman et al., 2005; Wang et al., 2007), however, tests of predictability have not been performed in many studies. Several techniques can be used for mathematical modeling. Some examples are: exponential models (Mollo and Corrigan, 2003), models based on percolation theory (Batycky et al., 1997; Ehtezazi and Washington, 2000), compartment models (Murty et al., 2004), Monte Carlo simulations (Barat et al., 2008), models based on convolution (Guse et al., 2006a), and Fourier analysis (Raiche and Puleo, 2006). Some examples of models used to describe drug release from PLGA-based DDSs are mentioned in this section, but as these techniques are not the subject of this review, the reader is referred to other review articles on this topic (Arifin et al., 2006; Siepmann and Göpferich, 2001; Siepmann and Siepmann, 2008).

The most famous of the empirical/semi-empirical mathematical models is the Peppas equation (Peppas, 1985):

$$\frac{M_t}{M_\infty} = kt^n \quad (1)$$

where M_t is the amount of drug released at time t, M_∞ is the total amount of drug encapsulated, k is a constant incorporating characteristics of the system and n is the release exponent. The value of n may be indicative of the release mechanism. For a purely diffusion-controlled, non-swelling, and non-degrading system, and a constant diffusion coefficient, $n = 0.5$ for a thin film, 0.45 for a cylinder and 0.43 for a sphere. Other values of n are indicative of purely swelling-controlled systems. Exponents between the values consistent with purely one-factor-controlled systems describe a form of transport referred to as anomalous transport, which may include other types of phenomena than swelling and diffusion. The Higuchi equation and the Hopfenberg model are other examples of empirical models (Siepmann and Göpferich, 2001; Siepmann and Siepmann, 2008). The Weibull equation is another example, and is suitable for sigmoidal drug release profiles (D'Souza et al., 2005). Duvvuri et al. (2006) used three different empirical equations to describe sigmoidal or tri-phasic release from microspheres with different PLGA blends. They obtained good fit between experimental data and the model, and the results indicated that some PLGA blends had a higher density. These and similar empirical/semi-empirical equations have been used in discussions on the release mechanism (Gagliardi et al., 2010; Liu et al., 2003; Yen et al., 2001; Zidan et al., 2006) and to calculate the diffusion coefficient (Alexis et al., 2004). However, conclusions can only be drawn if the assumptions associated with the equations are fulfilled, for example, constant diffusion coefficient and no erosion. This may be the case when using a hydrophobic and high-M_w PLGA that swells and degrades at a negligible rate compared to the rate of diffusion through an initially continuous porous network. However, more dynamic PLGAs are commonly used, and after a period of degradation, slowly swelling and degrading high-M_w PLGAs become rapidly swelling and degrading low-M_w PLGAs. In such cases, the diffusion coefficient cannot be assumed to be constant.

Mechanistic models describing drug release are often based on diffusivity as described by Fick's law. Some models utilize a constant effective diffusion coefficient, while in others, the effective diffusion coefficient is a function of another parameter. Wang et al. (2007) used a constant diffusion coefficient, but included the processes dissolution, drug crystallization and drug–excipient complex binding. Lemaire et al. (2003) used two different diffusion coefficients: one for diffusion from micropores to initially existing larger pores and one for diffusion in these larger pores. The lat-

ter coefficient was much higher than the first. According to this theory drug release was determined by the rate of transport to the larger pores, which was governed by either diffusion or erosion. Hsu et al. (1996) used the Roseman-Higuchi model for a cylindrical system to calculate the constant diffusion coefficient, as they argued that polymer erosion had little influence on drug release during the release period. They encapsulated isoniazid in two different DDSs: dry-mixed matrices, in which the drug particles were connected like drug-filled channels, and in PLGA foams, in which the drug particles were separated by polymer regions. The release was studied *in vitro* at different temperatures. When diffusion occurs through a solid phase, the diffusivity can be related to the Arrhenius expression, and the natural logarithm of the diffusion coefficient is proportional to $1/T$ (where T is the temperature in Kelvin). Diffusion in a liquid can instead be described by the Stokes–Einstein equation, combined with the Carrancio equation, which describes the relation between viscosity and temperature. The natural logarithm of the diffusion coefficient is then instead proportional to D/T. Plotting $\ln(D)$ against D/T and $1/T$ led to the conclusion that isoniazid diffused through water-filled pores in the dry-mixed matrices and through the polymer phase in the foams.

The mechanistic models describing erodible systems often utilize a chemical reaction to describe the effect of polymer degradation and/or erosion. Many of these models include a non-constant diffusivity or permeability parameter, which is an advantage. Siepmann et al. (2005) simulated the effective diffusion coefficient as a function of particle size to illustrate the effect of auto-catalysis on diffusion. The classical Higuchi model was modified by Heller and Baker who introduced a permeability parameter that increased with time as more pores were created (Arifin et al., 2006). The same time-dependent effective diffusion coefficient and the constant k characterizing the polymer degradation rate (Eq. (2)), was used to describe the drug release from PLGA films and microspheres in two separate studies (Berkland et al., 2004; Charlier et al., 2000). In a study of 5-fluorouracil release from microparticles of PLGA, a relationship was found between the diffusion coefficient and the polymer M_w (Eq. (3)) (Faisant et al., 2002). Another such mathematical relationship has been found in a study on a small hydrophobic drug (Eq. (4)) (Raman et al., 2005).

$$D_{eff}(t) = D_0 \times e^{kt} \tag{2}$$

where D_0 is the initial diffusion coefficient.

$$D(M_w) = D_0 + \frac{k}{M_w} \tag{3}$$

where k is a constant.

$$\ln(D) = -0.347x^3 + 10.394x^2 - 104.950x + 316.950 \tag{4}$$

where $x = \ln(M_w)$.

The Monte Carlo technique has been used to simulate polymer erosion and, combined with diffusive mass transfer, this technique could describe the release of 5-fluouracil from PLGA-based microparticles, and showed good agreement with experimental data (Fig. 5) (Siepmann et al., 2002). Limited drug solubility in the system was also taken into account. This model allowed the simulation of a time- and position-dependent diffusion coefficient, which is a great advantage. The model did not include a description of swelling or processes such as pore closure. However, these processes may be insignificant, considering that the high-M_w PLGA (104 kDa) used in the study exhibits a low degree of water absorption and polymer chain mobility during the first three weeks of degradation (Fredenberg, 2004), which was the duration of drug release.

The use of mathematical models in the evaluation of the physico-chemical processes governing drug release makes it possible to explain and predict the release process. A prerequisite is that the model is properly validated experimentally. If the model fits the experimental data, and particularly if its predictive power can be demonstrated, it is very probable that the conclusions drawn from the simulations are accurate. Another advantage is that it is possible to perform quantitative predictions of drug release. The disadvantage is that other possible explanations cannot be completely excluded. A model based on many parameters, which is often necessary for an accurate description, can be made to fit many different release profiles. There may be more than one set of parameters or equations that fit the experimental data. For example, a zero-order release pattern may depend on, and be modeled by, the rate of diffusion and the rate of polymer degradation/erosion. The decreasing concentration gradient and increasing diffusion distance, leading to a decrease in the rate of transport, may be counteracted by the increase in porosity resulting from erosion, leading to an increased rate of transport. However, the zero-order release may also be due to pore closure at a rate that counteracts the effect of pore formation. Another possible explanation may be that the transport resistance increases in one part of the system and decreases in another part (Fredenberg, 2011; Park, 1995). A study of leuprorelin release from one-month depot microspheres provides a good example of apparently zero-order release, attributed to superimposed first-order phases of diffusion and erosion is (Okada, 1997). In addition to diffusion and erosion, drug release was affected by the interaction between the cationic leuprorelin and the anionic PLGA, and the magnitude of this effect depended on the degree of degradation. Scanning electron microscopy (SEM) images showed increasing pore closure in the microspheres with time, which could affect the rate of drug release, although this was not mentioned. Furthermore, as the osmolality of the release medium was decreased, the rate of drug release increased, due to faster water absorption and possibly the formation of cracks due to osmotic pressure. This is an example of drug release being affected by many processes simultaneously, which would be difficult to simulate, although zero-order release was easily described mathematically, showing a good fit to the experimental data. Tests of predictability using independent experimental data are therefore an advantage.

Unfortunately, swelling is often ignored in mathematical modeling. DDSs have been classified as diffusion-controlled systems, swelling-controlled systems or erosion-controlled systems (Arifin et al., 2006). PLGA-based systems are mostly considered to be erosion-controlled systems, sometimes diffusion-controlled, while possible swelling often is ignored. The amount of water absorbed

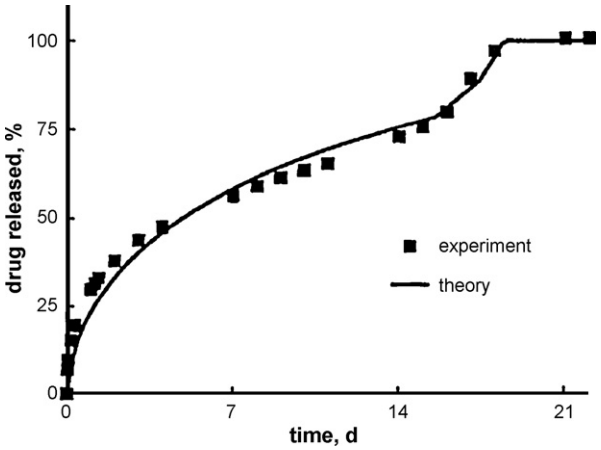


Fig. 5. Comparison of experimental data and a simulation of drug release based on the Monte Carlo technique of polymer erosion in combination with diffusive mass transfer.
Originally published by Siepmann et al. (2002).

is highly dependent on the properties of the PLGA, and swelling is sometimes insignificant. However, a large amount of water may be absorbed (Fredenberg et al., 2009; Kim et al., 2005), leading to the formation of pores, apart from erosion (Mochizuki et al., 2008; Webber et al., 1998).

A model is a simplification of the real system, and its applicability and suitability are restricted (Siepmann and Siepmann, 2008). As chemical reactions, mass transfer and other kinds of processes influencing drug release depends strongly on the characteristics of the DDS, it is crucial to choose an appropriate model for each DDS (Arifin et al., 2006; Siepmann and Göpferich, 2001). A suitable model with proven predictive power is an important tool in pharmaceutical development. Mathematical models can be very useful for the mechanistic understanding of drug release, but the assumptions made in modeling are very important, and the general application of mathematical models should be undertaken with care and preferably be substantiated by predictability tests.

4.3. Studying processes that enhance or hinder drug release

A third way of elucidating true and rate-controlling release mechanisms is to study processes that influence drug release. The drug release profile can be compared to the results of studying processes such as erosion, swelling, pore closure, pore formation, drug–drug interaction, and changes in the T_g. Another example of the way in which insight into drug transport can be gained is to study the heterogeneity/homogeneity of the polymer mass and the location of high transport resistance (Fredenberg, 2011). Examples of studies and the conclusions drawn are presented below.

Park (1995) found that a surface layer with low porosity controlled the rate of mass transfer until it cracked. The PLGA microspheres had two glass transition temperatures: one decreased with time while the other remained constant, until it disappeared. This suggests that there were two regions degrading at different rates, and it is likely that the rapidly degrading area was in the interior due to the pH gradient. The fact that the microspheres retained their shape and integrity until they disintegrated completely indicates that the slow-degrading region was at the surface, which suddenly broke. This coincided with the disappearance of crystallized degradation products, indicating that the surface acted as a semi-permeable diffusion barrier, allowing small molecules such as water to enter, but not the crystallized degradation products to be released, until the build-up of osmotic pressure was so high that the surface broke.

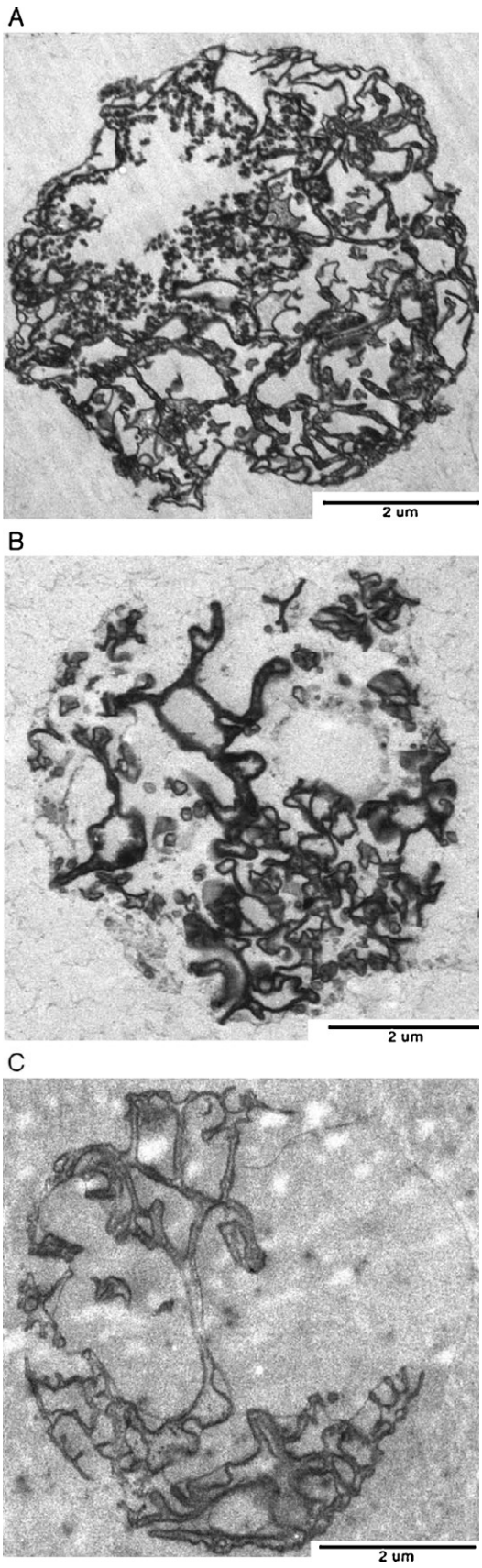
Pore closure, ending burst release and probably affecting subsequent drug release, has been demonstrated in a study of porous microspheres (Wang et al., 2002). The permeability was studied using fluorescent probes and confocal microscopy. The encapsulated drug exhibited a burst release on the first day. SEM analysis clearly showed the closure of pores at the surface. In addition, fluorescent probes in the release medium were initially able to diffuse into the microsphere, but not after 24 h. In another, but methodologically similar, study this pore-closing phenomenon was found to be affected by the incubation temperature, as temperature influences the mobility of the polymer chains and their ability to rearrange (Kang and Schwendeman, 2007).

The ability of the additives to act as porogens and affect the porous structure appeared to determine the release rate in a study on the effect of different additives on drug release using SEM analysis and erosion measurements (Song et al., 1997). Without additives, the drug release profile showed a slow release period followed by a faster release period, which coincided with an increasing rate of erosion. Thus, the release mechanism seemed to be diffusion through water-filled pores, with increased rate of diffusion at a later stage due to pore formation caused by erosion. Water-soluble additives increased the porosity and changed the release profile to one approaching zero-order, while a water-insoluble additive decreased the rate of drug release, making it more similar to the erosion profile. The additives affected the porous structure in addition to polymer erosion, and the rate of drug diffusion was determined by the porous structure.

Polymer–drug interactions were found to affect drug release in a study on the release of amoxicillin from cylinders of PLGA or PLA. Polymers with different molecular weights and L:G ratios were studied together with measurements of erosion, decrease in M_w, and nuclear magnetic resonance (NMR) (Mollo and Corrigan, 2003). The analyses showed that the presence of the drug decreased the rate of hydrolysis, and the effect was greater for the high-M_w and lactide-rich polymers. The fraction of intact drug released increased with polymer M_w and with the drug load. These findings indicate that the drug, or its degradation products, may bind or cross-link to the polymers. This phenomenon was less pronounced with higher-M_w PLGAs, as there are fewer polymer chain end groups, and at higher drug load, as there were probably more drug molecules than polymer end groups. Interactions between the drug and PLGA were supported by NMR.

Drug release seemed to be predominantly governed by connected channels formed by the presence of the drug, in a study of the release of ovalbumin (OVA) from PLGA microparticles (Zhao and Rodgers, 2006). A rapid release phase was followed by a period of zero-order release, and there was no lag phase, which is common for 75:25 PLGA with an M_w of 68 kDa, as it swells and degrades slowly (Fredenberg, 2004). Initial high porosity would cause rapid release. However, the surface of the microparticles seemed to be non-porous when analyzed with SEM. OVA was stained and its location within the microparticles was monitored during drug release using transmission electron microscopy (TEM). It was found that connected pores filled with OVA existed initially (Fig. 6). These pores may initially have been too small for detection using SEM analysis, and there may have been few connections with the surface. This investigation showed that swelling and degradation/erosion did not play an important role in drug release. It was also found that the protein distribution was not completely homogeneous initially, and release from some parts of the particle was faster than from others.

The transport resistance and rupture of the shell structure seemed to govern the release of cisplatin from microparticles consisting of a core of PLGA and cisplatin, and an outer shell of PLA (Matsumoto et al., 2006). Different release profiles were found depending on the M_w of the PLA shell. An almost-zero-order drug release, which was identical to the profile of the erosion of the PLGA core, was found for 10 kDa PLA. This result alone indicates erosion-controlled drug release. However, when the shell consisted of a mixture of 10 and 110 kDa PLA (5:1), the drug release surprisingly increased between days 4 and 7. This mixture absorbed less water, as measured in the study, and is known to degrade slower. However, microscopic studies revealed rupture of the higher-M_w shell, probably due to high water absorption and swelling of the PLGA core. The ruptures were observed at the same time as the drug release increased. These findings suggest that the shell constituted a significant part of the total transport resistance. The transport resistance in the PLA shell, in contrast to the degradation kinetics of the PLGA core, may have determined the release of PLGA core degradation products, which would result in the similar profiles for drug release and PLGA erosion. The molecular weight of cisplatin (300.1 Da) is in the same range as water-soluble PLGA degradation products (up to 1100 Da), which means that the rate of diffusion should be similar, based on the M_w. In a similar study, PLA shells of a different M_w that did not rupture were used (Matsumoto et al., 2005). From studies of drug release, polymer erosion and SEM analysis, drug release was concluded to consist of four steps: (i) a burst of drug molecules at the surface, (ii) drug release through pores



in the PLA shell, (iii) erosion of the PLGA core and (iv) diffusion through more effective pores in the PLA shell.

Studying processes that enhance or inhibit drug release could, of course, also be combined with mathematical modeling in order to elucidate the true and rate-controlling release mechanisms. Faisant et al. (2002) used different analyses, such as differential scanning calorimetry, size exclusion chromatography and SEM, to identify the processes taking place before developing a mathematical model that allowed the quantitative description of drug release.

The third technique that can be used to obtain a mechanistic understanding discussed in this section, i.e. studying specific processes that may influence drug release, has the advantage that it provides detail knowledge on drug release. The disadvantage of this technique is that pre-knowledge regarding the system may be required in order to decide what to study. As with mathematical modeling, identifying some processes that explain drug release does not exclude the possibility of other processes affecting the system. However, as in the case with mathematical modeling, when there is agreement between different results, for example, a simultaneous increase in the rate of drug release and the appearance of cracks, it is very unlikely that another unobserved process governs drug release. When there is no detailed knowledge of the system, it is a good idea to perform a general analysis of the DDS and follow, for example, drug release, degree of native drug release, water absorption, polymer M_w, erosion, the porosity, and the size and shape of the DDS. Most of these analyses are inexpensive and easy to perform. The knowledge gained is important as it contributes small pieces to the complex puzzle of drug release and is helpful in pharmaceutical development.

5. True and rate-controlling release mechanisms

As mentioned in Section 2, many physico-chemical processes have been reported as the dominating release mechanism or rate-determining process. One reason for this is the different use of the term "release mechanism" by researchers. Another reason is the complexity of drug release from PLGA-based DDSs, as discussed in Section 3 and illustrated in Figs. 2 and 3. The true and rate-controlling release mechanisms are discussed in this section, and examples of studies that support or disprove them are given.

5.1. True release mechanisms

As mentioned in Section 2, there are four true release mechanisms:

- diffusion through water-filled pores,
- diffusion through the polymer,
- osmotic pumping, and
- erosion (no drug transport).

Diffusion through water-filled pores has been mentioned as the release mechanism countless times (Gao et al., 2007; Yushu and Venkatraman, 2006; Zidan et al., 2006). In many studies, this release mechanism has only been used to describe the first stage of the release period, before the onset of polymer erosion (Alexis et al., 2004; Johnson et al., 1997; Lam et al., 2000). However, diffusion describes the *way* in which the drug is released, while in these cases

Fig. 6. TEM images of OVA-loaded microparticles during degradation. The samples were stained with osmium and then post-stained with a mixture of uranyl acetate and lead citrate before TEM analysis. The 80 nm slice was cut from approximately half the diameter of the particle. Protein distribution is represented by dark areas. (A) 20 days; (B) 40 days; (C) 60 days.
Originally published by Zhao and Rodgers (2006).

erosion is a process that influences the *rate* of diffusion. There are also examples of complete drug release before any significant polymer erosion (Liu et al., 2005; Patel et al., 2008; Sansdrap and Moës, 1997). The burst release phase is sometimes said to be diffusion dependent. In a study on the release of a highly water-soluble drug from microspheres, the drug release was reported to be proportional to the square root of time, during the burst phase, which is indicative of diffusive transport (Lee et al., 2002).

Diffusion through water-filled pores is very dependent on the porous structure of the polymer, and is therefore dependent on the processes that promote pore formation and pore closure. The effective diffusion coefficient is dependent on the diffusion coefficient in the fluid in the pores, the porosity and the tortuosity (Cussler, 1997). Pores must also be continuous from the drug molecule to the surface of the DDS and sufficiently large for the solute to pass through. Dead-end pores, too small pores and the degree of connection between pores influence the porosity and the tortuosity. Constant diffusion coefficients for drugs encapsulated in PLGA-based DDSs are more likely to be found in cases of small and initially porous particles consisting of high-M_w, hydrophobic and slowly swelling and degrading PLGAs, with low polymer chain mobility. Pore-forming processes, i.e. erosion and swelling, will have greater effects on low-M_w and less hydrophobic PLGAs, and on large or non-porous particles. For example, in a study of the release of human growth hormone (hGH) encapsulated in porous microspheres of slow-degrading semi-crystalline PLA, it was found that hGH was completely released before any significant erosion had taken place. However, the release of hGH encapsulated in non-porous PLGA particles was slower and more dependent on pore-forming processes (Kim and Park, 2004). Mathematical modeling has been used to confirm purely diffusion-controlled drug release from PLGA-based DDSs. In a study on the release of pyranine encapsulated in a core of tri-glycerides, and coated with PLGA, the release was found to be purely diffusion-controlled, as the release profile could be described by an analytical solution of Fick's second law for cylinders, after a lag phase of 20 days (Guse et al., 2006b). The lag phase could be due to the time before polymer erosion or water absorption had formed continuous pores of sufficient size. However, as the release could be described using a constant diffusion coefficient, further enlargement or formation of more pores did not seem to be dominating processes. Perhaps the rates of pore formation and pore closure were equal. In another study of 5-fluorouracil release from PLA fibers, diffusive drug release was also concluded by the use of mathematical modeling. Polymer erosion was much slower than drug release in this study (Gao et al., 2007).

There are many different factors that may influence the rate of drug diffusion. However, as long as the drug molecules are released due to transport, diffusion through water-filled pores is the true release mechanism throughout the whole release period, unless diffusion takes place in the polymer or the drug transport is driven by osmotic pressure. As the encapsulated drug is often a large hydrophilic molecule, not able to diffuse through the polymer, and the osmotic pressure is often compensated for by polymer swelling, diffusion through water-filled pores is usually the main true release mechanism.

Diffusion through the polymer is possible for small hydrophobic drugs (Raman et al., 2005; Wiscke and Schwendeman, 2008). For example, the small hydrophobic drug ropivacaine, was completely released from PLGA microspheres *in vivo* after 8 h, which is before the onset of polymer erosion. Some of these molecules could have been detached from the surface, but it is unlikely that none of the drug molecules would have been properly encapsulated using the spray-drying method (Ratajczak-Emselme et al., 2009).

Unlike diffusion through water-filled pores, diffusion through the polymer is not particular dependent on the porous structure. However, the drug must be dissolved in water before being released, and this process could decrease the overall release rate. High porosity increases the surface area for drug dissolution and could thus enhance drug release. Kang and Schwendeman (2003) used confocal microscopy to determine the diffusion coefficient of bodipy, a small hydrophobic molecule, which partitioned strongly to the polymer. The diffusion coefficient did not increase as PLGA degraded or when the pore-forming substance $MgCO_3$ was encapsulated together with bovine serum albumin (BSA). However, the diffusion coefficient varied considerably with the temperature. These results clearly indicate that most diffusion took place in the polymer, although pores were created and diffusion was faster in the pores. The strong partitioning of bodipy to the polymer explained the constant diffusion coefficient, and it was concluded that the porous structure was not important.

The rate of diffusion through a polymer is very dependent on the physical state, and for a small molecule, may increase by several orders of magnitude at the transition from the vitreous to the rubbery state (Karlsson et al., 2001). T_g is above 37 °C for the original polymer. However, upon immersion in water at 37 °C, the plasticizing effect of water usually transfers the polymer into the rubbery state (Blasi et al., 2005; Ricci et al., 2005). A very high-M_w PLGA may remain in the vitreous state for a while before degradation and water absorption affect the polymer. The glass transition temperature of PLGA in a DDS may also be lower than that of the original polymer due to degradation during the manufacturing process and the plasticizing effects of additives or residual water (Passerini and Craig, 2001; Spenlehauer et al., 1989). Drug diffusivity through the polymer is often higher in lower-M_w polymer, as the polymer chains are more flexible (Faisant et al., 2002; Ricci et al., 2005; Wiscke and Schwendeman, 2008). As mentioned in Section 4.2, different mathematical relationships have been found between the diffusivity and polymer M_w. It has also been reported that PLGA microparticles may undergo structural relaxation after transition to the vitreous state during manufacturing, which means that the polymer chains become closer, and the microparticles become denser (Allison, 2008). This process, which often takes place during storage, may be a source of batch-to-batch variability. As in the case of diffusion through water-filled pores, the diffusion coefficient will be less variable in high-M_w PLGAs, with small particles. Degradation will play a greater role in low-M_w PLGAs, and with large particles. For example, the release of estradiol by diffusion through low-M_w PLGAs was found to follow zero-order, as a result of increasing diffusion coefficient due to degradation. The use of high-M_w PLGAs lead to release profiles which could be described by the Higuchi equation, i.e. a constant diffusion coefficient (Mittal et al., 2007).

Osmotic pumping is a phenomenon that occurs when osmotic pressure, caused by water absorption, drives the transport of the drug. The nature of the transport is then convection and not diffusion, as discussed in Section 2. This release mechanism is more common for DDSs using materials other than PLGA. However, there have been some reports of osmotic pumping from PLGA-based DDSs. One example is a hollow cylindrical DDS of PLA using polyethylene glycol (PEG) as a porogen to create pores (Jonnalagadda and Robinson, 2000). The cylinder was filled with either 5-fluorouracil (5FU) or fluorescein isothiocyanate (FITC) dextran and then sealed with a viscous PLA solution. Release of 5FU followed an equation describing diffusion-controlled transport. However, the release of FITC dextran was not dependent on the dextran M_w, as is the case for diffusive transport, and a linear relationship was seen between the release rate and the osmotic gradient. From the analyses of this DDS it was concluded that the system functioned mainly as an osmotic pump. Another example is a DDS of PLGA (85:15) containing a reservoir space filled with the drug basic fibroblast growth factor (bFGF) and the osmotic agent PEG (Ryu et al., 2007). Narrow channels connected the reservoir

and the surface of the DDS. Water was taken up through the channels and an osmotic pressure was built up in the reservoir as PEG was dissolved, and this pumped the drug out through the channels. Osmotic transport was found to depend on the length of the channels, while diffusive transport depended on both the length and the area. Osmotic transport dominated when the channels were longer than 60 μm. In both of these examples, osmotic agents and pores or channels were used for drug transport. A requirement for transport to be driven by osmotic pressure is that the influx and efflux of water are equal, after an initial period of water content adjustment. The polymers used in both examples were very hydrophobic, as the L:G ratios were high (100:0 and 85:15), and the molecular weights were very high (324 kDa and inherent viscosity (IV) = 2.3). The rate of water absorption through such polymers and thus the swelling are minimal, and it is possible to maintain an equal water influx and efflux and osmotic pressure. These polymers degrade very slowly, and degradation and erosion are negligible during the drug release period. However, most PLGA-based DDSs consist of lower-M_w PLGAs, which swell significantly sooner or later, and any osmotic pressure will then be compensated for by the increase in volume. Osmotic pressure caused by water absorption may result in rupture of the polymer. However, osmotic pumping is not a common release mechanism for PLGA-based DDSs.

Erosion, as a true release mechanism, i.e. drug release without drug transport, results in identical profiles of drug release and polymer erosion, assuming that the drug is homogeneously distributed throughout the DDS. Identical drug release and polymer erosion has been reported although such reports are rare. In a study on the release of testosterone and BSA from PLGA films, the drug release profiles were identical to the polymer mass loss profile (Fig. 7), at least up to 60% release of BSA, after which the release of BSA leveled off (Shah et al., 1992). In another study, the release profiles of levamisole from PLGA discs and polymer erosion were reported to be almost identical (Fitzgerald and Corrigan, 1996). As mentioned in Section 2, degradation/erosion is frequently reported as a *rate-controlling* release mechanism, i.e. the process controlling the rate of diffusion, often during the final period of drug release (Grayson et al., 2004; Wang et al., 2004a; Westedt et al., 2006; Zilberman and Grinber, 2008). Polymer erosion could cause drug molecules very close to the surface to be released without transport, and the release mechanism would then be erosion. However, as hydration is normally much faster than erosion, it is more probable that the drug will diffuse through pores formed by water absorption. Erosion could be the main release mechanism for low-M_w PLGA formulations, in which a significant part of the polymer has a molecular weight just above the limit for water solubility. However, as remnants of the polymer are commonly reported after complete drug release (Cleland et al., 1997; Faisant et al., 2002), erosion is rarely the dominating true release mechanism.

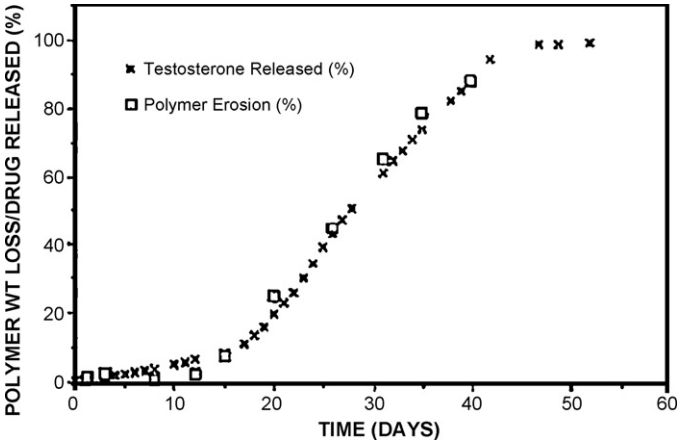


Fig. 7. Comparison of the release of testosterone and polymer erosion of PLGA films. Originally published by Shah et al. (1992).

The encapsulated drug may be released by more than one true release mechanism simultaneously, and the dominating mechanism may change with time. Diffusion is not only dependent on the diffusion resistance inside the polymer matrix. Diffusion through an unstirred layer surrounding the DDS may lead to a significant transport resistance. The concentration in the surrounding bulk can also inhibit drug diffusion from the DDS. Sink conditions and sufficient stirring are of special concern for hydrophobic drugs with low water solubility, as the concentration may easily reach saturation (Wiscke and Schwendeman, 2008).

5.2. Rate-controlling release mechanisms or processes that enhance or inhibit drug release

Water absorption or *swelling* occurs immediately upon immersion in water or administration *in vivo*. This has been found to create pores in the polymer matrix (Mochizuki et al., 2008; Webber et al., 1998), increasing the rate of drug diffusion. However, swelling may also cause pore closure in low-M_w and relatively hydrophilic PLGAs with high polymer chain mobility, as swelling may enable the rearrangement of the polymer chains and the formation of a homogeneous swollen polymer mass without distinct pores (Fredenberg et al., 2011). Water absorption causes hydrolysis, but it also increases the pH inside a DDS and reduces the acid catalytic effect on hydrolysis. Swelling was found to cause burst release in a study in which drug release was monitored using confocal microscopy, pore size was analyzed using SEM and the diffusion of water was measured using NMR (Messaritaki et al., 2005). Desai et al. (2010) found a relationship between drug release and water absorption. In a study on the effect of $Mg(OH)_2$ on the release of BSA from PLGA millicylinders, it was found that the salt increased the release rate, due to increased water absorption and porosity (Zhu and Schwendeman, 2000). However, water absorption does not always have a significant effect on drug release. Song et al. (1997) found no direct correlation between the water absorption capacity and drug release.

Dissolution of the drug could determine the rate of release, if it is slower than the rate of transport. Wong et al. (2001) found that a model describing both drug diffusion and dissolution fitted the experimental data for human immunoglobulin G release from PLGA microspheres during the first 50 days better than a model describing diffusion only. Dissolution is, however, rarely reported as the rate-controlling process, probably as encapsulated drugs have, to date, usually been relatively hydrophilic, for example, proteins and peptides. However, the trend towards more pharmaceutical substances of very low solubility will make the dissolution process more important.

Hydrolysis has been found to be important regarding drug diffusion through the polymer (Charlier et al., 2000; Raman et al., 2005). The release rate and the diffusion coefficients have been linked to the M_w in several studies, as described in Section 4.2. In a study on the release of hGH encapsulated in PLGA films, which normally takes place in water-filled pores, mathematical relationships were found between the polymer M_w and the release of hGH (Santoveña et al., 2006). Relationships could only be established for a certain period of the drug release, and these periods differed for different formulations. During diffusion through water-filled pores, it is likely that hydrolysis affects another process which, in turn, affects the rate of diffusion, for example, water absorption and erosion. Both these processes are pore forming, and depend on the M_w of the polymer. Diffusion through the polymer depends on polymer chain mobility and density, which are affected by the M_w. Hydrolysis is a process that strongly influences other processes that may

enhance or inhibit drug release, as shown in Fig. 2, and discussed further below.

Heterogeneous degradation due to the auto-catalytic effect is well known. As mentioned in Section 4.3, Park (1995) reported two glass transition temperatures, one originating from the rapidly degrading interior, and one originating from a slowly degrading region close to the surface. The former decreased with time while the latter remained constant. This surface layer did not become porous as the interior, and acted as a diffusion barrier, until the barrier appeared to have burst due to the build-up of osmotic pressure. The formation of a less porous layer, due to heterogeneous degradation, thus controlled drug release. The microspheres investigated were about 10 μm in diameter, and heterogeneous degradation, with a porous interior and a less porous surface layer, has also been observed in thin films 10 μm thick in another study (Lu et al., 1999). Berkland et al. (2007) found a surprisingly slow release of fluorescein-dextran from non-porous PLGA microspheres, which is attributable to heterogeneous degradation. The interior became hollow, while the surface remained non-porous, or showed low porosity. This morphological development was also observed in another study on the release of a hydrophobic model drug (Mao et al., 2008).

Changes in polymer chain mobility and density affect the rate of diffusion through the polymer, as discussed in Section 5.1. Polymer chain mobility and density is affected by hydrolysis and plasticization of the polymer, and by crystallization of oligomers trapped inside the matrix.

The crystallization of oligomers decreases the rate of transport of the drug, the dissolved degradation products and water. The crystallization of oligomers has been reported to occur (Vert et al., 1991) but, to the best of our knowledge, no study has been performed demonstrating that this process actually determines the rate of drug release.

Erosion, or polymer mass loss, has been reported to start at an average M_w of 15 kDa (Husmann et al., 2002). Erosion as a true release mechanism has been discussed in Section 5.1. Erosion as a rate-controlling release mechanism leads to pore formation, which increases the rate of diffusion. Dissolved degradation products trapped inside the DDS can affect the processes influencing drug release in many ways, for example, by catalyzing hydrolysis, by increasing the rate of water absorption due to increased osmolality, and by plasticization of the polymer. As these degradation products are lost during erosion, so are their effects, which means that erosion could theoretically inhibit drug release. However, the dominating effect of erosion is increased drug release and, as mentioned in Section 2, there are numerous reports of erosion governing drug release, especially during the later part of the release period.

Pore formation is a process governed by water absorption and polymer erosion, as mentioned in Section 3, or may be caused by the release of a porogen. The rate of drug release from PLA films has been found to be associated with the presence of open pores at the surface (Mochizuki et al., 2008). In a study on the effect of morphology on drug release, porous, non-porous and porous particles with covered pores at the surface were prepared. Drug release was found to be governed by the initial porous structure during the first period of drug release (Bae et al., 2009). Pore formation is an important process, as the encapsulated drug is often a large hydrophilic substance, usually released by diffusion through water-filled pores.

Pore closure has been observed in several studies, and is likely to affect the release rate. This phenomenon has been demonstrated, by the use of confocal microscopy together with fluorescent probes and SEM analyses, to be the explanation of the cessation of burst release (Wang et al., 2002). Kang and Schwendeman (2007) suggested that pores may open and close during the release period, and thus alternately trap and release drug molecules. They argued that the diffusivity in water should lead to rapid drug release, even for large molecules, due to the short diffusion pathways in microspheres, even those with high tortuosity. Disregarding polymer–drug or drug–drug interactions, diffusion through water-filled pores can be inhibited by low porosity, insufficient pore size (Fredenberg et al., 2004) or pore closure. In one of our recent studies, the diffusion of glucose, a small, inert hydrophilic molecule, through a highly swollen PLGA film was found to be very slow (Fredenberg, 2011). The explanation of this slow diffusion therefore seems to lie in the transport properties of the DDS, and not in the properties of the diffusing molecule. Pore closure is related to polymer chain mobility and rearrangement. Examples of different factors that have been found to induce or affect pore closure, and also polymer chain mobility, are polymer degradation, plasticizing agents and increased temperature (Badri Viswanathan et al., 2001; Berkland et al., 2003; Bouissou et al., 2006; Kang and Schwendeman, 2007; Okada, 1997). The collapse of porous microparticles, and thus pore closure, has been observed when the (constant) incubation temperature had reached the so-called critical softening point, which was 10–20 °C higher the decreasing T_g (Friess and Schlapp, 2002). In one of our studies we observed pore closure at the surface of porous PLGA films being degraded under different conditions. Pore closure was especially rapid at low pH (3.0) (see Fig. 8) (Fredenberg et al., 2011). The pH may be important as it may be low inside PLGA matrices, and *in vitro* and *in vivo* (Anderson and Shive, 1997; Díez and de Ilarduya, 2006; Ding and Schwendeman, 2008; Sastre et al., 2007). The polymer contracted and separated from water at low pH, and we suggested that pore closure was caused by a hydrophobic effect, due to the higher hydrophobicity of PLGAs with a low degree of polymer carboxyl acid dissociation at low pH. The more hydrophobic nature of the polymer was confirmed by measurements of water absorption and wettability (contact angles). This result is in agreement with findings in a study on burst release from microspheres incubated in a buffer of pH 4. Water absorption was slower, pore closure was more rapid, and the burst release was decreased upon co-encapsulation of a small amount of glucose in porous microspheres (Wang et al., 2004b). According to the authors, polyols are known to increase the surface tension of water which, according to our findings, was part of the mechanism of pore closure at low pH. Our findings could also explain the results of a study on the release of Huperzine A from PLGA microspheres. The rate of drug release and the rate of water absorption were slower during incubation in a buffer of pH 4.0 than of 7.4 (Liu et al., 2005). In our study, pore closure also occurred at pH 7.4, although it was slower. At pH 7.4, the polymer was more hydrophilic and swelled considerably. We suggested that pore closure was caused by the diffusion of mobile polymer chains, forming a homogeneous, swollen polymer–water mass, instead of distinct regions of either polymer or pores. It should be noted that the M_w of this PLGA was relatively low, and that the rate of pore closure, or lack of detectable closure, was related to the M_w and the degree of hydrophobicity of the polymer (Fredenberg et al., 2011). Berkland et al. found a surprisingly slow release of BSA from initially porous microspheres. The microspheres became hollow with time, while the pores at the surface closed. This was probably one reason for the slow drug release, although drug–polymer interactions or drug–drug interactions could not be ruled out (Berkland et al., 2007). Pore closure and pore formation are two simultaneously ongoing processes, and in our study we found that pore closure occurred rapidly at pH 3.0 and pH 7.4, while pore formation dominated at pH 5–6 (Fredenberg et al., 2011). The complexity of the processes taking place in PLGA matrices result in microenvironmental heterogeneity throughout the matrices. The difference in polymer chain mobility and pH may be the cause of porous and non-porous regions. Another factor that may affect the processes on a submicron level is the curvature at polymer–water interfaces,

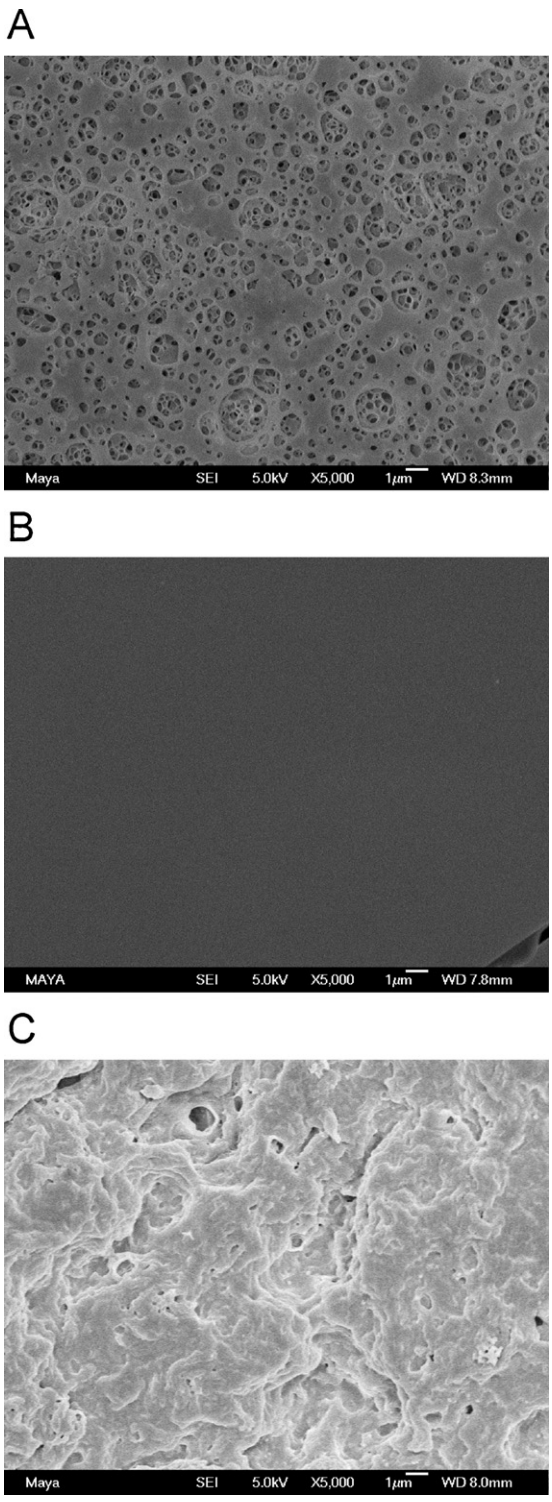


Fig. 8. Porosity at the surface of PLGA films after two days of pore-forming pretreatment (A), and after five more days of degradation at pH 3.0 (B) or pH 7.4 (C). Picture A constitutes a part of a figure in a paper by us (Fredenberg et al., 2011).

which are known to affect physico-chemical properties, such as solubility, according to the Ostwald ripening phenomenon (Ratke and Voorhees, 2002).

Polymer–drug interactions have been found to influence the release rate (Okada, 1997). In two separate studies, the release of L-asparaginase in one and the release of BSA in the other, were found to be slower from nanoparticles of an uncapped polymer than from a capped, but otherwise identical PLGA, although capping decreased the rate of degradation (Blanco and Alonso, 1997; Gaspar et al., 1998). This was attributed to the interaction between the drugs and the uncapped terminal carboxyl groups. Ionic interaction between lidocaine and PLGA was also proposed as the probable explanation of the slower release of lidocaine than ibuprofen in a study on PLGA particles and films (Klose et al., 2008). The adsorption of drug molecules to the polymer is undesirable, as it may lead to incomplete release (Butler et al., 1999; Crotts et al., 1997). A protein may also lose its biological function due to chemical reactions, such as deamidation and acylation in acidic environments (Houchin et al., 2006; Ibrahim et al., 2005; Zhang et al., 2009). Ketoprofen was found to plasticize PLGA by hydrogen binding (Blasi et al., 2007), which may enhance or inhibit drug release. As the environment inside PLGA matrices varies with time and position, so may the degree of polymer–drug interactions. These interactions may be responsible for the release of only a certain proportion of the drug molecules and perhaps only for part of the release period.

Drug–drug interactions, such as the formation of physical or covalent aggregates, have been suggested to be the cause of slower and incomplete drug release (Wong et al., 2001; Zhu and Schwendeman, 2000). Such aggregates are also the result of an acidic environment (Kang et al., 2008). As in polymer–drug interactions, the influence of drug–drug interactions may vary with time and position according to the microenvironment.

The formation of cracks in the DDS may affect the release rate. Rapid water absorption could result in polymer rupture, which should of course increase the release rate. The above mentioned study regarding heterogeneous degradation, during which a surface diffusion barrier was formed, is another example of the probable formation of cracks. The surface barrier allowed water penetration, and then seemed to disappear (Park, 1995). Another example is the study mentioned in Section 4.3, in which rupture of the PLA shell surrounding the drug–PLGA core increased the rate of drug release. Before rupture, drug release followed the course of polymer erosion (Matsumoto et al., 2006).

Collapse of the DDS may enhance drug release, as new surfaces may be created and fragments of the DDS may fall off (Friess and Schlapp, 2002). It may also inhibit drug release, due to a decrease in porosity (Díez and de Ilarduya, 2006). Collapse is often the result of degradation and the decrease in T_g, and is often associated with particle aggregation (Park et al., 1995). Aggregation could lead to slower drug release due to a decrease in surface area, or faster drug release, as the acid gradient and the catalytic effect on degradation would increase. However, it is not obvious that aggregated particles are particularly densely packed. The diffusion pathway of high transport resistance may still be short, and the surface area for drug release inside the agglomeration of aggregated particles may still be sufficient, and therefore only have a minor effect on drug release.

Many of the rate-controlling release mechanisms may affect drug release simultaneously, and the dominant mechanism may alter during the release period. The dominant mechanism may also differ between different microparticles in the same system. Particles of different sizes are prone to different degrees of auto-catalytic degradation. Cracks may be formed on some particles but not on others. As mentioned in Section 4.3, the release rate of OVA from different regions of a microparticle differed, according to TEM (Zhao and Rodgers, 2006). This demonstrates the heterogeneous nature of PLGA matrices. When a process is taking place at a particular place in the matrix, the effect will be local, and as one process may influence others, regions with different characteristics may arise.

Some of these processes affect drug release in more than one way. For example, hydrolysis leads to erosion and pore formation, and thus an increase in drug release. However, hydrolysis also leads to a lower T_g, possible rearrangement of polymer chains, and pore closure, and thus possibly a decrease in drug release. More opposing effects are given in Table 4. The impact of one process on drug

Table 4
Processes that may increase or decrease the rate of drug release.

Process	Possible effect	Effect on the release rate
Hydrolysis	Auto-catalysis	Increase
	Erosion and pore formation	
	Plasticizing effect of oligomers	
	Crystallization of oligomers	Decrease
	Polymer chain mobility and pore closure	
	Drug–drug and polymer–drug interactions	
Erosion	Pore formation	Increase
	Loss of catalytic effect of acidic degradation products	Decrease
Water absorption	Hydrolysis	Increase
	Pore formation	
	Increased pH	Decrease
	Polymer chain mobility and pore closure	
Collapse of the polymer structure	Cracks and new surfaces	Increase
	Decreased porosity	Decrease

release may be altered when other processes or the environment are changed. For example, the solubility of the drug, drug–drug interactions, polymer–drug interactions, hydrolysis, pore formation and pore closure, all depend on the pH, which depends on the rate of hydrolysis, water absorption and transport out of the system. The different factors that influence these processes, sometimes in more than one way, add to the complexity. For example, a soluble basic salt with divalent cations may: (i) decrease the rate of hydrolysis by neutralizing acids, (ii) create pores due to the pore-forming effect of divalent cations, probably caused by the catalysis of hydrolysis, (iii) create pores due to water absorption caused by increased osmolality, and (iv) act as a porogen. The situation becomes even more complicated due to the fact that it may be difficult to predict the actual *in vivo* environment. However, the complexity of the system also means that there are many possible ways to solve a particular problem. Each arrow in Figs. 2 and 3, demonstrating the complexity, is also a potential way of modifying drug release, and there are thus many ways of obtaining a suitable DDS.

6. Conclusions and future outlook

PLGA has attracted much interest due to its potential as a drug carrier in the controlled release of encapsulated drugs, and is currently the most frequently used biodegradable polymer for this application. It is important to understand the release mechanisms, and which factors that influence the release rate, in order to be able to modify drug release. Many studies have been carried out on this subject. The term release mechanism has been used with different meanings, and the definition of the term has been discussed in this review. The term can refer to the *way* in which a drug is released or to a process that determines the *rate* of drug release. We suggest that processes describing the way the drug is released should be denoted *true* release mechanisms. Processes influencing drug release are important, but should be discussed in terms of processes or *rate-controlling* release mechanisms, as they provide important information regarding the rate of drug release. True and rate-controlling release mechanisms have been studied in different ways, which are generally based on the shape of the release profile, mathematical modeling or studies on processes that influence drug release. All of these techniques have their advantages and disadvantages. Mathematical modeling gives a rapid general view and fundamental insight into the dominating release mechanism, or the processes influencing drug release. However, as PLGA systems are complex, models require a substantial experimental effort for model validation to make full use of the approach. Studying specific processes that influence drug release, for example, polymer erosion, pore closure or polymer–drug interactions, provides detailed knowledge of the system from which conclusions can be drawn regarding the release mechanisms and the dominating processes influencing the release rate. However, this method may be more time consuming than mathematical modeling, and the complexity should be considered when drawing conclusions.

We have discussed the release mechanisms and processes influencing drug release that have been reported in the literature. Controlled drug release from PLGA-based DDSs is complex, and many processes that influence drug release affect each other in many ways. The effects of different factors on drug release may vary in time and position through a polymer matrix. There are four true release mechanisms: (i) diffusion through water-filled pores, (ii) diffusion through the polymer, (iii) osmotic pumping, and (iv) polymer erosion (i.e. no drug transport). Diffusion through water-filled pores is the most common, as the encapsulated drugs used so far have mainly been large, relatively hydrophilic biopharmaceuticals, for example proteins and peptides.

The complexity of drug release from PLGA-based DDSs makes it difficult to generalize results obtained with specific DDSs. Although research with specific DDSs is necessary for product development, and insuring that controlled-release products actually reach the market, the findings may not be applicable to other DDSs. Simplified systems have the advantage of including fewer parameters, enabling studies on a specific parameter or process which should be applicable in several situations, although the dominant parameter or process may differ.

PLGAs with a wide range of physico-chemical properties are commercially available, and it is possible to tailor the release profile by the choice of PLGA. PLGAs can also be blended with other materials, and formulations can be mixed, for example, formulations displaying a slow sigmoidal release and a faster Fickian diffusive release. It may be difficult to predict drug release due to the complexity of the system, but there are many possible ways of modifying drug release. General, basic and mechanistic research can provide pieces of the full puzzle improving the possibility of rapidly solving problems during the development of controlled-release pharmaceuticals.

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