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Review

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

Susanne Fredenberg[a,*], Marie Wahlgren[b], Mats Reslow[c], Anders Axelsson[a]

[a] Department of Chemical Engineering, Lund University, P.O. Box 124, SE-221 00 Lund, Sweden
[b] Department of Food Engineering, Lund University, P.O. Box 124, SE-221 00 Lund, Sweden
[c] Novo Nordisk A/S, Novo Nordisk Park, DK-2760 Måløv, Denmark

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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

* Corresponding author. Tel.: +46 702 108465; fax: +46 462 224526.
E-mail address: susanne.fredenberg@chemeng.lth.se (S. Fredenberg).

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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)