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Review

Principles of encapsulating hydrophobic drugs in PLA/PLGA microparticles

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ABSTRACT

Injectable biodegradable and biocompatible copolymers of lactic and glycolic acid (PLGA) are an important advanced delivery system for week-to-month controlled release of hydrophobic drugs (e.g., from biopharmaceutical classification system class IV), which often display poor oral bioavailability. The basic principles and considerations to develop such microparticle formulations is reviewed here based on a comprehensive study of papers and patents from the beginnings of hydrophobic drug encapsulation in polylactic acid and PLGA up through the very recent literature. Challenges with the diversity of drug properties, microencapsulation methods, and organic solvents are evaluated in light of the precedence of commercialized formulations and with a focus on decreasing the time to lab-scale encapsulation of water-insoluble drug candidates in the early stage of drug development. The influence of key formulation variables on final microparticle characteristics, and how best to avoid undesired microparticle properties, is analyzed mechanistically. Finally, concepts are developed to manage the common issues of maintaining sink conditions for in vitro drug release assays of hydrophobic compounds. Overall, against the backdrop of an increasing number of new, poorly orally available drug entities entering development, microparticle delivery systems may be a viable strategy to rescue an otherwise undeliverable substance.

Contents

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1. Introduction

The modern microencapsulation of bioactive substances continues to be an important formulation strategy since its inception about 70 years ago. Starting first with the aim to protect vitamins from oxidation (Taylor, 1938) it took some decades until polylactic acid (PLA) and later its copolymers, e.g., poly(lactic-co-glycolic acid) (PLGA), were evaluated as biodegradable and biocompatible polymers for drug delivery (Kulkarni et al., 1971; Cutright et al., 1971; Brady et al., 1973; Yolles and Sartori, 1980; Laurencin and Elgendy, 1994; Ignatius and Cleas, 1996; Anderson and Shive, 1997). Although already patented (Boswell and Scribner, 1973) and initially described by others (Nuwayser et al., 1977; Gardner et al., 1977), Beck, Tice, and coworkers were among the first to intensively study the encapsulation of hydrophobic drugs, i.e., steroids, and focus on their efficiency in vivo (Beck et al., 1979, 1980, 1981, 1983a,b; Tice and Lewis, 1983; Hahn et al., 1983; Cowsar et al., 1985). Despite the clear significance of these findings, these very early papers commonly did not focus in detail on both the experimental methods and the underlying concepts and principles of drug encapsulation. At the same time, the initial patents and reports on the delivery of peptide therapeutics, mostly for luteinizing hormone-releasing hormone analogs, were also becoming available (Chang, 1976; Sanders et al., 1984; Redding et al., 1984; Kent et al., 1986; Okada et al., 1987; Shimamoto, 1987; Ogawa et al., 1988a).

In the present literature of polymeric drug delivery devices, most publications focus on the encapsulation of larger molecules, e.g., peptides, proteins, and DNA/RNA for potential use as vaccines or as long-acting release (LAR®) drug formulations. Importantly, some of these initiatives led to important pharmaceutical products and most of them are still on the market (e.g., Lupron Depot®, Zoladex®, Decapeptyl®, Eligard®, Enantone®, Trenantone®, Nutropin Depot®, and Profact®). However, the vast majority of new chemical entities are neither peptides nor proteins, but molecules with a low molecular weight. Although no precise data are available, it has been estimated that up to 40% of all new chemical entities show poor solubility (Straub et al., 2005). Particularly with the development of BCS class IV drugs with a low solubility and a low permeability, which exhibit low oral bioavailability, companies are frequently faced with the choice to either develop or discard the early stage compound. In order to expedite this decision, the question of alternative delivery technologies needs to be discussed in the early stages of drug development. For certain drugs that (i) have a broad therapeutic window, (ii) require a low daily dose, and (iii) are going to be used for the long-term treatment of disease, injectable controlled release depots such as drug-loaded biodegradable polymer microparticles, may provide such an alternative delivery strategy, potentially rescuing an otherwise undeliverable drug.

Despite the literature focussing on the considerable challenges with injectable depots for biomacromolecules (e.g., peptide/protein stability, high encapsulation efficiency, and undesired initial burst release; Schwendeman et al., 1996; Sinha and Trehan, 2003; Jiang et al., 2005; Tamber et al., 2005), hydrophobic small molecules are an extremely significant class of drug substances and pose unique challenges in their own right. Therefore, this review focuses on hydrophobic drugs and seeks to develop some guiding principles to examine and solve key issues of their encapsulation in, and release from, injectable PLA and PLGA microparticles.