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Designing multilayered particulate systems for tunable drug release profiles

Wei Li Lee [a], Pattara-orn Yu [a], Meiju Hong [a], Effendi Widjaja [b], Say Chye Joachim Loo [a,*]

[a] School of Materials Science and Engineering, Nanyang Technological University, 50 Nanyang Avenue, Singapore 639798, Singapore
[b] Process Science and Modeling, Institute of Chemical and Engineering Sciences, 1 Pesek Road, Jurong Island, Singapore 627833, Singapore

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ABSTRACT

Triple-layered microparticles comprising poly(D,L-lactide-co-glycolide, 50:50) (PLGA), poly(L-lactide) (PLLA) and poly(ethylene-co-vinyl acetate, 40 wt.% vinyl acetate) (EVA) were fabricated using a one-step solvent evaporation technique, with ibuprofen drug localized in the EVA core. The aim of this study was to investigate the drug release profiles of these triple-layered microparticles in comparison to double-layered (PLLA/EVA and PLGA/EVA) (shell/core) and single-layered EVA microparticles. Double- and triple-layered microparticles were shown to eliminate burst release otherwise observed for single-layered microparticles. For triple-layered microparticles, the migration of acidic PGA oligomers from the PLGA shell accelerated the degradation of the PLLA mid-layer and subsequently enhanced drug release in comparison to double-layered PLLA/EVA microparticles. Further studies showed that drug release rates can be altered by changing the layer thicknesses of the triple-layered microparticles, and through specific tailoring of layer thicknesses, a zero-order release can be achieved. This study therefore provides important mechanistic insights into how the distinctive structural attributes of triple-layered microparticles can be tuned to control the drug release profiles.

1. Introduction

Biocompatible and biodegradable polymeric microparticles have received significant interest in the drug delivery field for the past few decades [1,2]. This is because they have the potential to optimize drug concentration at the site of action over prolonged periods. However, there are several inherent limitations on the use of conventional single-layered microparticles in drug delivery, which include burst release caused by the presence of entrapped drug particles on the surface [3], the inability to provide zero-order release and limitations in controlling drug release profiles and kinetics [4–7].

To better control the drug release rates of polymeric microparticles, the tailoring of the structural composition (e.g. multilayers, multicompartmental particles) of the polymeric matrix was thus introduced [4,8–12]. The use of multilayered or multicompartmentalized microcapsules also allows for simultaneous multiple drug delivery in biomedicine [11,13,14]. The release of encapsulated substance from polyelectrolyte-multilayer and multicompartmental capsules had been demonstrated by using various triggering mechanisms, such as laser light and ultrasound [15,16]. On the other hand, it had been reported that drugs localized within the inner cores of double-layered microparticles prepared by the solvent evaporation technique showed a reduction in burst release, while providing a sustained drug release profile [17,18]. Though studies of drug release from double-layered microparticles have been reported, achieving a desirable drug release profile with optimal release kinetics still remains very much a challenge, and no such studies have been conducted using triple-layered microparticles. The development of triple-layered or even multilayered microparticles can be an important step towards a versatile and robust approach to control the drug release rates, while having the capabilities of delivering multiple drugs (polypharmacies) from the same microparticle, where some layers contain drug substances; others are rate-limiting layers. Multilayered microparticles could be envisioned to provide pulsatile or time-delayed drug release kinetics, such as in the case of delivering vaccines. In addition, drug delivery to the small intestine or colon can be achieved using multilayered microparticles with an enteric shell, while housing multiple drugs in other layers for controlled release. It would also appear that delivery of radiosensitizers and/or anticancer drugs simultaneously through the use of multilayered microparticles would be attractive for cancer therapy. Furthermore, multilayered particulate devices could also be used as scaffold materials to deliver bioactive molecules to cells for tissue engineering. Nevertheless, the large size of the multilayered microparticles is a hindrance for intravenous injection, and surgical operations become a necessity for implantation.

Previous studies have shown that the degradation behavior of multilayered systems differed from that of a monolithic system [19–21]. It was thus postulated that triple-layered microparticles would possess uniquely different hydrolytic degradation

* Corresponding author. Tel.: +65 6790 4603; fax: +65 6790 9081.
E-mail address: joachimloo@ntu.edu.sg (S.C.J. Loo).

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