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Drug transport mechanisms and in vitro release kinetics of vancomycin encapsulated chitosan-alginate polyelectrolyte microparticles as a controlled drug delivery system

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ABSTRACT

In this study, chitosan-alginate polyelectrolyte microparticles containing the antibiotic, vancomycin chloride were prepared using the ionotropic gelation (coacervation) technique. In vitro release and drug transport mechanisms were studied concerning the chitosan only and alginate only microparticles as a control group. Further, the effect of porosity on the drug transport mechanism was also studied for chitosan-alginate mixed particles produced by lyophilizing in contrast to the air-dried non-porous particles. According to the in vitro release data, alginate only and chitosan only microparticles showed burst release and prolonged release respectively. Chitosan-alginate lyophilized microparticles showed the best-controlled release of vancomycin with the average release of 22 μg per day for 14 days. Also, when increasing alginate concentration there was no increase in the release rate of vancomycin. The release data of all the microparticles were treated with Ritger-Peppas, Higuchi, Peppas-Sahlin, zero-order, and first-order kinetic models. The best fit was observed with Peppas-Sahlin model, indicating the drug transport mechanism was controlled by both Fickian diffusion and case II relaxations. Also, Fickian diffusion dominates the drug transport mechanism of all air-dried samples during the study period. However, the Fickian contribution was gradually reducing with time. Porosity significantly effects the drug transport mechanism as case II relaxation dominates after day 10 of the lyophilized microparticles.

1. Introduction

Microparticles (MPs) have been extensively studied for the past few decades as a targeted drug delivery device in tissue engineering applications. Targeted drug delivery leads therapeutic agents in a site specific manner to a particular cell type or tissue (Patri et al., 2005). Generally, biocompatible and biodegradable polymers have been widely used for MPs preparation. The most commonly used biodegradable polymers, such as poly(L-lactide) (PLA) and poly(D, L-lactide-*co*-glycolide) (PLGA), cause toxicological effects due to the presence of organic solvent in the formulation methods (Caetano et al., 2016). Therefore, natural polymers such as chitosan and sodium alginate are widely used in drug delivery systems due to their relatively simple ionic cross-linking methods, as described in elsewhere (Anal and Stevens, 2005; Caetano et al., 2016; Gombotz and Wee, 1998; Liu et al., 1997; Mantripragada and Jayasuriya, 2016; Pasparakis and Bouropoulos, 2006). Chitosan, a deacetylated form of chitin extracted from crustacean shells, is a linear polysaccharide, composed of *N*-acetyl glucosamine (free amino groups) and glucosamine linked in a β (1–4) manner. The ratio between glucosamine/*N*-acetyl glucosamine is known as the degree of deacetylation (DD) (Di Martino et al., 2005; George and Abraham, 2006). Chitosan is usually insoluble in aqueous solutions above pH 7 but, because of the protonation of the free amino groups in glucosamine, chitosan dissolves in dilute acid solutions (pH < 6). Alginate is also a linear polysaccharide extracted from brown algae, but unlike chitosan, it dissolves in aqueous solutions. It contains a varying amount of 1–4 linked α-L-guluronic and β-D-mannuronic acid residues (Gombotz and Wee, 1998; Pasparakis and Bouropoulos, 2006). Moreover, alginate has the ability to form gels by reacting with divalent cations such as Ca^{2+}, Sr^{2+}, and Ba^{2+} under an extremely mild environment (George and Abraham, 2006).

There are two major types of bone infections namely osteomyelitis and septic arthritis. The main reasons for these types of bone infections are open fractures due to high energy trauma (e.g., Gunshot wound, motor vehicle accidents) and joint arthroplasty (Cevher et al., 2006). Most commonly, these types of bone infections are caused by *staphylococci*, a Gram-positive organism. Vancomycin, a broad spectrum glycopeptide antibiotic, is active against Gram-positive organisms. In

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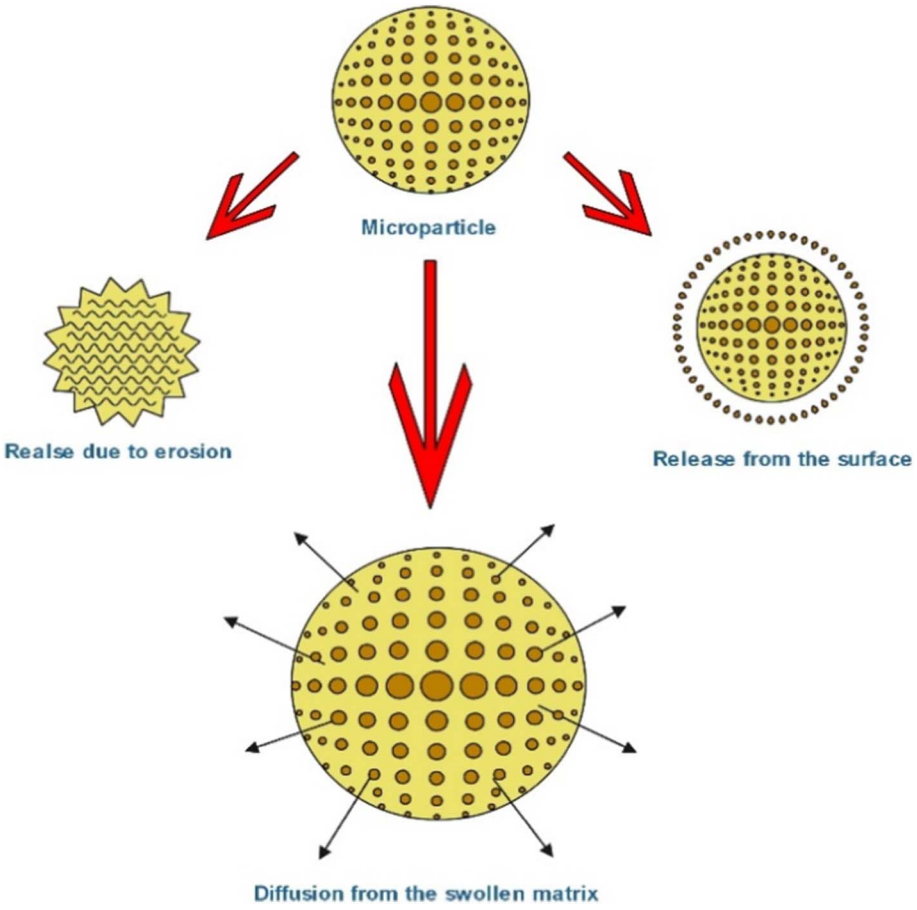

Fig. 1. Mechanism of drug release from particulate system.

previous studies, vancomycin encapsulated MPs were successfully used against *Staphylococcus aureus* (Cevher et al., 2006) and *Staphylococcus epidermidis* (Mantripragada and Jayasuriya, 2016). According to Liu et al. (Liu et al., 2006), microencapsulation is defined as a method of storing solid, liquid, or gaseous substances in miniature, sealed capsules that can release their contents at controlled rates under specific conditions. The main advantage of the biodegradable drug delivery system is that it will eliminate the need for additional surgery to remove the drug carrier. Also, the targeted drug delivery system uses a significantly less amount of drugs, as it reduces the side effects and improves the efficiency due to the localized release (Gbureck et al., 2008).

The drug release from polymer particulate system involves three different mechanisms: (i) release due to polymer erosion, (ii) diffusion through the swollen matrix, and (iii) release from the surface of particles (Agnihotri et al., 2004; Fredenberg et al., 2011). The schematic diagram of three mechanisms is shown in Fig. 1. In most of the situations, drug release is driven by more than one mechanism. The release from the surface of the particle leads to burst release effect and drugs entrapped in the surface layer also follows this effect. This burst release can be avoided by washing MPs with water of proper solvent after crosslinking process, or by increasing the crosslinking density. However, these methods reduce the encapsulation efficiency of the drug (Agnihotri et al., 2004). Apart from the previously described three mechanisms, the chemically controlled drug release mechanism is also possible in polymer hydrogel system. In this type of situation, drug (or molecules) release is determined by the chemical reactions occurring between the polymer network and releasable drug (Lin and Metters, 2006). The knowledge of release kinetics is essential for the efficient use of the drug delivery system. The release of drug from delivery systems depends on many physical and chemical properties of both drug and the carrier, such as porosity, surface roughness, chemical composition, molecular weight, degradation rate, particle size, the amount of the pharmaceutical dosage form, and drug-matrix interaction (Costa and Lobo, 2001; Gbureck et al., 2008).

Most commonly used kinetic model in drug release studies is the Ritger-Peppas model (Ritger and Peppas, 1987a) (also known as power law). This model has been successfully used by numerous researchers for past few decades to describe the drug transport through Fickian diffusion and anomalous transport (Gbureck et al., 2008; Huang and Brazel, 2001; Li et al., 2008; Pasparakis and Bouropoulos, 2006; Raval et al., 2011; Serra et al., 2006; Shi et al., 2011; Siepmann and Peppas, 2001). Apart from this model, Higuchi model (Carbinatto et al., 2014; Raval et al., 2011; Serra et al., 2006), zero order model (Li et al., 2008; Liu et al., 2006; Serra et al., 2006; Yao and Weiyuan, 2010), first order model (Borges et al., 2006; Carbinatto et al., 2014; Yan et al., 2017), and Peppas-Sahlin model (Liu et al., 2006; Serra et al., 2006; Siepmann and Peppas, 2001; Yao and Weiyuan, 2010) were successfully used to describe the drug release mechanisms from polymer particulate systems.

The primary objective of this research work is to develop an injectable drug delivery system for the controlled release of vancomycin and study the drug transport mechanism of that system. According to the preliminary studies, we found that vancomycin release from chitosan MPs was relatively low and not suitable for drug delivery system. Also, alginate MPs showed burst release of vancomycin. So, we tried to combine those low and high drug release of low molecular weight (MW) chitosan and alginate MPs respectively by making chitosan-alginate mixed MPs. Even though these type of MPs were studied for the decades, very few studies have been conducted on drug transport mechanisms. Therefore, we examined the drug release mechanism of chitosan-alginate mixed MPs with respective to the chitosan alone and alginate alone MPs. Also, we were interested in elucidating the effect of