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The role of polymer/drug interactions on the sustained release from poly(DL-lactic acid) tablets

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Abstract

The release profiles of model drugs (propranolol HCl, diclofenac sodium, salicylic acid and sulfasalazine) from low molecular weight poly(D,L-lactic acid) [D,L-PLA] tablets immersed in buffer solutions were investigated in an attempt to explore the mechanism of the related phenomena. It was confirmed that drug release is controlled by diffusion through the polymer matrix and by the erosion of the polymer. The pH of the surrounding medium influences the drug solubility as well as swelling and degradation rate of the polymer and therefore the overall drug release process. Physicochemical interaction between D,L-PLA and drug is an additional factor which influences the degree of matrix swelling and therefore its porosity and diffusion release process. Propranolol HCl shows extended delivery time at both examined pH values (5.4 and 7.4) and especially at pH 7.4 where release was accomplished in 190 days, most probably due to its decreased solubility at higher pH values. The acidic drugs gave shorter delivery times especially at pH 7.4. A slower drug release rate and more extended delivery time at pH 7.4 in comparison with that at pH 5.4 was recorded for tablets loaded with diclofenac sodium and salicylic acid. The opposite effect was observed with samples loaded with propranolol HCl.

Keywords: Biodegradable polymers; Poly(lactic acid); Sustained drug release; Erosion; Swelling

1. Introduction

Poly(DL-lactic acid) has been extensively used for making systems for delivery of therapeutic substances, including contraceptive steroids, anti-cancer drugs, anti-malarial agents, peptide hormones etc. The drugs can be incorporated either as dissolved or dispersed phase into the polymeric matrix which degrades in contact with the biological fluids, which allows a progressive release of the drug content. Various configurations of drug release devices, including microspheres [1], rods [2], films [3] and nanoparticles [4], have been fabricated from PLA to control the drug release with suitable modification in polymer composition, crystallinity, molecular weight and structure.

Three mechanisms for controlling drug release from these systems have been proposed [5]: (a) Fickian diffusion through the polymer matrix, (b) diffusion through water filled pores created upon

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swelling of the matrix and (c) delivery by erosion of the polymer matrix. A combination of these mechanisms with contribution of surface burst effect has also been claimed to explain the release profile [6].

It was reported that polymer–drug interaction plays a significant role on the drug release behaviour of the examined delivery system. For acidic drugs, faster hydrolysis of ester bond is expected, due to acid catalysis. For basic drugs two effects can be observed: base catalysis of the ester bond cleavage [7], and neutralization of carboxy end groups of polymer chains which restricts the autocatalytic effect of acidic chain ends. Thus degradation can be accelerated or retarded by a base, depending on the relative contribution of the above two effects [8,9].

In previous papers [10,11] the swelling/erosion behaviour of low molecular weight DL-PLA produced by direct polycondensation of lactic acid was presented and discussed. The effect of the nature of the incorporated drug was also taken into consideration.

In this work, the following drugs were studied as model reactive compounds in matrix delivery devices, because they represent typical pharmaceutical molecules with different physicochemical properties: propranolol hydrochloride, diclofenac sodium, salicylic acid and sulfasalazine.

Propranolol HCl is used to treat certain cardiovascular disorders and hypertension. Polymeric carriers such as hydroxypropylmethylcellulose (HPMC) tablets [12] and nanoparticles made of poly-*e*-caprolactone (PCL), poly(lactide-*co*-glycolide) (PLGA) or ethylcellulose [13], were used for preparation of systems capable to control the release profile and to provide more effective therapies.

Diclofenac sodium is a non-steroidal anti-inflammatory drug (NSAID) suitable for treatment of arthritis disorders, such as ankylosing spondylitis, rheumatoid arthritis and osteoarthritis. Side effects of NSAIDs administration result in the gastrointestinal mucosal damage, irritation and bleeding. On the other hand, the administration of NSAIDs into the intra-articular cavity in patients with chronic inflammatory disease is complicated due to the short duration of the effect. Parenteral administration through PLGA microspheres provides sustained release of diclofenac and reduces the localized gastrointestinal disturbances due to the frequent oral administration of the drug [14].

It should be noted that diclofenac shows the following two important characteristics. First, its solubility depends on the pH of the surrounding solution and, secondly, it undergoes an intramolecular cyclization under the acidic conditions found in gastric liquids, which can cause its inactivation [15]. The controlled release of diclofenac from tablets made of HPC [16] and the combined system ethylcellulose and chitosan [17] were also studied.

Salicylic acid, an acidic drug, is the key additive in many skin-care products for the treatment of acne, keratosis pilaris and warts. The controlled-release of salicylic acid has been studied using different types of formulations, such as PLA tablets [18], poly(ethylene oxide) (PEO) hydrogels [19], microballons [20], films made of chitosan and polyalkyleneoxide-maleic acid copolymer [21].

Sulfasalazine is an acidic drug, used to treat diseases of the colon, such as irritable bowel syndrome, Crohn's disease and ulcerative colitis. For the treatment of inflammatory bowel disease, regular intake of anti-inflammatory drugs and daily administration of high drug doses are required. Therefore controlled release devices such as capsules, tablets, microparticles have been developed, capable of delivering the drug specifically to the colon in order to reduce the total administered dose to the patient and to decrease their possible adverse effects [22,23].

In this work, further study on the delivery of the above substances incorporated in a biodegradable i.e. D,L-PLA tablets, was performed. Their release behaviour at different pH environments was explained taking into consideration the polymer/drug interaction, the PLA swelling/erosion behaviour and the solibility of each drug.

2. Materials and methods

2.1. Materials

Low molecular weight D,L-PLA (M_v: 2500) was prepared by direct polycondensation of lactic acid, in an inert atmosphere according to the procedure described in [24]. Samples of PLA were loaded with 2% propranolol hydrochloride (ICI, UK), Diclofenac sodium (Sigma, UK), Salicylic acid (Fluka, UK) and Sulfasalazine (Sigma, UK). Some of the physicochemical parameters of these drugs are listed in Table 1.

2.2. Preparation of samples and measurements

The drugs were added and mixed into the melt of PLA. After incorporation, the melt was moulded