Sustained release of guaifenesin and ipriflavone from biodegradable coatings

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Abstract

Biodegradable plastics are an interesting class of drug carriers for controlled release, as they can decompose to non-toxic, readily bioresorbable products and are advantageous over conventional biomaterials because they do not require surgical retrieval from the body after completion of treatment. In this work, films of poly(D,L-lactic acid) (D,L-PLA) were deposited by the solvent casting technique, onto the surfaces of stainless steel plates and their biodegradation was studied after immersion in buffer solutions. The release of two model drugs, i.e. guaifenesin and ipriflavone, from the above D,L-PLA systems loaded with these compounds at various concentrations, was also studied.

The experimental results showed that for low drug concentrations, the release of guaifenesin is controlled by the biodegradation rate of PLA, whereas for high concentrations the burst effect becomes the dominant release mechanism. The rate of release is faster at low pH values probably due to an acceleration of PLA biodegradation, whereas there are no chemical interactions between drug and polymer, that could essentially influence the release rate of the drug or the biodegradation of the polymer. On the other hand, high guaifenesin concentrations produce increased porosity in the PLA matrix and seem to accelerate its biodegradation and further the drug release rate. Finally, the release of ipriflavone in a mixture of 2-propanol/water is clearly a two stage process and, again, the burst effect seems to control the delivery process at high drug concentration.

In conclusion, the present study shows that similar results to those obtained with D,L-PLA tablets loaded with model drugs can be obtained with thin coatings of the same systems. This might be of interest for transfer of the existing knowledge to the design of biomedical implants, treated with coatings of D,L-PLA containing reactive compounds.
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1. Introduction

The drug delivery devices, aiming at the "zero order release", which guarantee a constant rate of drug administration with time, can be divided into the following categories [1,2]:

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- Matrix devices, prepared by uniform dispersion of drug particles throughout a solid non-erodible polymer [3].
- Bioerodible systems, i.e. polymers or blends susceptible to degradation when in contact with living tissues [4–6].
- Swelling control units, deriving from dissolution or dispersion of a drug into a polymer matrix, that swells when immersed in water.

Recent developments in the area of sustained release of drugs have shown the great importance of biodegradable plastics. In fact, these materials once implanted, decompose to nontoxic, readily bioresorbable products and therefore they do not require surgical retrieval from the body after completion of the release.

Among biodegradable polymers, poly(lactic acid) (PLA) is perhaps the most extensively studied material for this application. It undergoes scission in the body to monomeric units of lactic acid, which is a natural intermediate in carbohydrate metabolism. PLA is therefore suitable for further uses such as resorbable sutures, implants for orthopedic surgery or blood vessels, which finally can be replaced by the body's tissues. As to the sustained release, PLA has been used for delivery of antimycobacterial drugs [7], quinolones [8], antimalarial and antiinflammatory drugs [9], antitumor agents [10], hormones [11] and fluoride containing tablets for oral use [12].

In the above literature, the investigations on biodegradation and release have been made by the use of PLA tablets, and therefore, it seemed interesting to further explore this area by running experiments with PLA films deposited on metal substrates. This would be an interesting aspect of biomedical products based on metallic implants, such as stents, that may need a biodegradable coating with the suitable drug to promote compatibility with human body after implantation. On the other hand, due to the small thickness of the film, it might be interesting to explore the contributions of the release due to drug diffusion in combination with that deriving from biodegradation. Moreover, for the same as above reason, the burst effect taking place during the early stages of release from PLA, could greatly affect the overall release profile in this particular case of thin biodegradable films. In this research the following pharmaceutical compounds were selected as model drugs for the experimental set up:

(a) Guaifenesin (GFN), a drug widely used to promote lower respiratory tract drainage, and
(b) Ipriflavone, a synthetic flavonoid derivative.

Studies of the delivery of GFN have been made using polymeric films as carriers, such as polyethylene oxide (PEO), by hot-melt extrusion process. It was found that concentration of GFN up to 30% led to crystallization of the drug on the film surface which is important for the burst effect [13].

GFN was also used as a model drug in polylactic acid (PLA) and poly(ester amide) (PEA) systems [14]. Very interestingly, the release from PLA films was found to take place in a biphasic manner, with an initial fast release stage followed by another of slower release. The initial fast rate was attributed to a release of the drug incorporated at or near the surfaces of the polymeric films. The second phase can be explained by a combination of two mechanisms: diffusion through the films and hydrolytic degradation of PLA. It was also recorded that GFN release was much faster from PLA than from the PEA films due to a lag-time observed in the latter case.

Further research, showed that the neutral GFN has no significant effect on the degradation rate of D,L-PLA, and although GFN is quite hydrophilic the water uptake of GFN containing D,L-PLA films was lower than that of drug-free D,L-PLA film [15].

As to ipriflavone, a substance used to improve osteoblast cell activity inhibiting bone resorption [16], very low release rates were recorder in experiments using polyvinyl chloride (PVC) matrix tablets as carriers. The release mechanism of this slightly soluble drug from PVC matrix is the result of tablet erosion, and therefore, methyl-cellulose (MC) derivatives, polyvinyl-pyrrolidone and lactose were added to the above compositions to increase the rate of release [17]. Monolayer composite systems, with potential use of local administration into the periodontal pocket, made of poly(D,L-lactide-co-glycolide) (PLGA) micromatrices loaded with ipriflavone and embedded in a chitosan film, were prepared and studied for their release characteristics. The micromatricial structure of films was found to offer good morphological characteristics, such as thickness and flexibility useful for periodontal pocket delivery. Furthermore, these systems offer the advantage of micromatricial structure combined with the mucoadhesive properties of chitosan and the prolonged release properties of PLGA [18].