DEVELOPMENT OF SLOW RELEASE HIGHLY WATER SOLUBLE DRUG DELIVERY SYSTEM

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INTRODUCTION

New drug delivery systems offer numerous advantages compared to the conventional dosage forms such as modified release of active substance (Freitas et al., 2005, Freiberg et al., 2004), protection of encapsulated materials against oxidation and humidity (especially important for hygroscopic drugs), masking of undesirable odor or taste of active ingredient (Silva et al., 1999), improved efficacy, as well as improved patient compliance and convenience (Berchane et al. 2007).

Microencapsulation of highly-water soluble drugs is a challenge especially if low molecular weight component must be encapsulated. The high hygroscopicity of the currently produced cardioprotective drug mildronate (3-(2,2,2-trimethylhydrazinium)propionate dihydrate) defines additional requirements to both the packaging material and the storage conditions that is why up to now only conventional dosage forms of mildronate – capsules and sterile solution – are manufactured. Taking into account growing interest in prolonged administration of mildronate an attempt was made to prepare modified release form of the drug.

An appropriate selection of the polymer matrix is necessary in order to develop successful drug delivery system. In the present study polylactide (PLA), polystyrene (PS) and polyhydroxybutyrte (PHB) were tested for controlled delivery of highly-water soluble mildronate. The effect of polymer choice on the final product was investigated and release rate of active component from microparticles was evaluated.

EXPERIMENTAL METHODS

Materials

Poly(L-lactide) (Biomer L9000) with molecular weight of 200-300 kDa, PS with molecular weight of 50-300 kDa and polyvinyl alcohol (PVA) with molecular weight of 25 kDa and 98 mol % hydrolyzed were both purchased from Polysciences (Warrington, USA). PHB with molecular weight of 200 kDa was supplied from Biocycle. Mildronate was a gift from JSC Grindex (Latvia). All solvents were distilled before use.

Preparation of PHB/mildronate microparticles

50ml of 1% polyhydroxybutyrate solution in chloroform was mixed with 10ml of saturated mildronate solution. Then the disperse phase formed was emulsified in 30ml of a 0.5% polyvinylalcohol water solution and stirred for 10min, heating continuously the reaction medium and supplying inert gas therein. After 20min, the product obtained was separated by filtration and dried.

Preparation of PLA/mildronate microparticles

Polylactide (1g) was dissolved in 10ml of dichloromethane. Mildronate (1g) was dissolved in 0.5ml of water. PVA (4g) was dissolved in 100 ml of water. An aqueous solution of mildronate was added to the polymer solution in dichloromethane. W_1/o primary emulsion was properly mixed and added to 100 ml of 4% aqueous PVA solution. After emulsification, the organic solvent was extracted in 3.5l of water. Then the microcapsules formed were separated by filtration and dried.

Preparation of PS/mildronate microparticles

Polystyrene (1g) was dissolved in 10ml of dichloromethane. Mildronate (1g) was dissolved in 0.5ml of water. PVAl (4g) was dissolved in 100ml of water. An aqueous solution of mildronate was added to the polymer solution in dichloromethane. The w_1/o primary emulsion was properly mixed and added to 50ml of a 4% aqueous PVA solution. After emulsification, the organic solvent was extracted in 3.5l of water. Then the microcapsules formed were separated by filtration and dried.

Scanning Electron Microscopy

Examination of surface morphology and internal morphology was done using SEM Mira\LMU scanning electron microscope.

X-ray diffractometry

Powder X-ray diffractometry (PXRD) patterns were recorded on a PANalytical X'Pert PRO diffractometer.

RESULTS AND DISCUSSION

The effect of polymer type on the total drug load, encapsulation efficiency, particle size distribution, repeatability of microencapsulation process (evaluated as standard deviation between six replicate experiments) was evaluated and results are summarized in Table 1 below.

Table 1: Characterization of microparticles.

	PHB/ mildronate	PLA/ mildronate	PS/ mildronate
Total drug load, %	77	45	39
Repeatability, %	2	4	3
Encapsulation efficiency, %	25	58	61
Particle size, µm	200-300	200-400	150-200

The evaluation of the surface morphology of PHB/mildronate microparticles has shown that almost the whole surface of the microsphere is covered with tiny crystals of mildronate indicating that PHB/mildronate microspheres is not suitable for preparation of a slow release drug delivery system. Taking into account the microparticles' morphology, these formations can be classified as matrix type microcapsules or microspheres (see Figure 1 a and b).

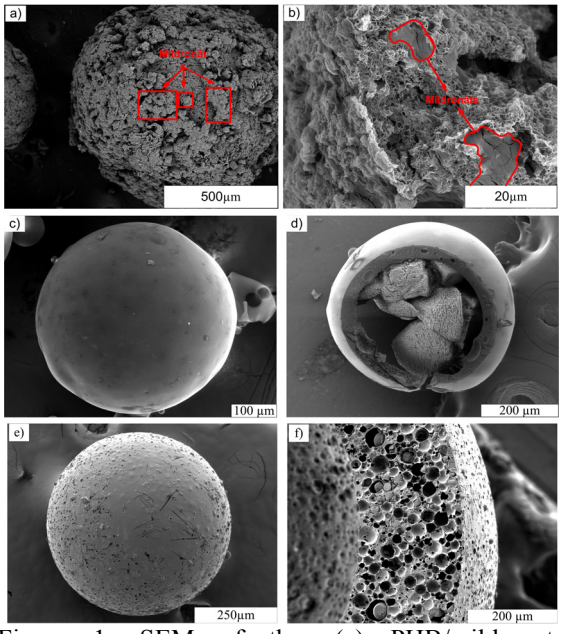

Figure 1: SEM of the: (a) PHB/mildronate microspheres (b) cross-section of PHB/mildronate microspheres (c) PS/mildronate microcapsules (d) cross-section of PS/mildronate microcapsules (e) PLA/mildronate microcapsule (f) cross-section of PLA/mildronate microcapsules.

PS/mildronate microparticles have a round shape and a smooth surface. According to the microparticle morphology, PS/mildronate preparations can be classified as mono-cored or one domain microcapsules, in which the whole active ingredient is located inside the polymeric coating (see Figures 1 c and d).

In the case of polylactide matrix, the obtained microparticles consist of the non-homogenous mixture of the polymer and mildronate as well as several active ingredient loaded domains from 2µm to 45µm in diameter. According to the microparticle morphology, PLA/mildronate preparations can be classified as multi-domain microcapsules (see Figure 1 e and f).

The X-ray diffraction scans showed that the drug-PLA and drug-PHB systems, in the form of microcapsules, indicated the presence of the crystalline drug, and PXRD scans were identical to those of the physical mixture. It was suggested that, during the process of drug crystallization from the water solution, a specific crystalline lattice of the active ingredient was formed.

A dramatic decrease in the diffraction intensity can be observed for PS/mildronate microcapsules. This could be explained by the microcrystallization of mildronate in the PS matrix, when the active ingredient concentration exceeds its solubility in the polymer.

During the study it was found that the microencapsulation process parameters and the selected polymer matrix affect not only the encapsulation efficiency of the active ingredient and the total drug load, but also the morphology and granulometric composition of microparticles.

The use of PLA, PHB and PS matrices in long-term experiments decreased the hygroscopicity of mildronate but only polystyrene matrix ensured delayed release of mildronate in single dose (*in vivo*) experiments, not affecting the total amount of the released active ingredient.

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