Branched polyesters as mucoadhesive carriers of drugs

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Introduction

Copolymers of lactic acid and glycolic acid, marked as PLGA, have their significant place in pharmacotherapy as drug carriers. Very little is known about mucoadhesion of star-like copolymers PLGA, branched on polyhydric alcohols. Unlike linear polyesters, these are endowed with a low gyration diameter[1)] and a low degree of swelling. The biodegradation rate of these polymers runs continuously over several hours to several days depending on the molecular weight parameters[2)]. Sufficiently low viscosity can be achieved by dissolving in a suitable solvent, or by their plasticizing. Hydrophilic plasticizers are released from the polymeric system after administration in the moment of exposure to body fluids which can accelerate the degradation rate of polymer and the drug release. Plasticizers with limited miscibility with water remain in the polymer system longer and ensure more standard conditions for drug release. In our work, we study thermal, rheological, mucoadhesive, and drug release properties of branched polyesters intended as drug carriers.

Experimental methods

Branched polyester was synthesized at the workplace of authors from the equimolar mixture of lactic acid and glycolic acid, and various polyols as the central branching monomer. Several esters of organic acids as plasticizers. Various organic solvents were employed for drug incorporation. Incorporation of drug into the unplasticized polyester was carried out by dissolution at first of polyester, and then of drug in the particular selected solvents. Incorporation of drug into the plasticized polyester was carried out by melting of the polyester in a hot-air drier at the temperature of 90 °C, the heated plasticizer in concentrations of 10%, 20%, 30%, or 40% was added, and the mixture was homogenized thoroughly.

A differential scanning calorimeter was used for the thermal analysis of the polyester carrier, plasticized polyester, drug, and their blends. Rheological characteristics of the polymer systems were measured on a Malvern Kinexus Pro$^+$ Rheometer using cone upper geometry 2°/20 mm with solvent trap at the shear rate range from 0.10 to 10.00 s $^{-1}$at three different temperatures (25.0; 37.0; 50.0 °C). The tensile test *in vitro* was employed for testing of mucoadhesivity of the plasticized polyester. Mucin from the porcine stomach, Type III, was used as the model substrate. The maximal force for detachment of the tested material from the model substrate was determined using the Material testing machine (Zwick/Roel) with modified equipment for adhesive testing. 500.0 mg of polymeric matrix were applied on the mucin substrate spread on a support with an absorptive surface. The support was placed into a vessel containing 50.0 mL of phosphate citrate buffer pH 7.4. The sealed vessel was then immersed into a shaking water bath maintained at 37 °C, and allowed to shake at a constant frequency for 50 min^{-1} and with an amplitude of 22 mm. At stated time intervals the dissolution medium was withdrawn and replaced. Drug released was determined by HPLC.

Results and discussion

We have synthetized PLGA branched various concentrations of the branching monomer in the reaction system provided polymers with different parameters. The polyester with molar mass M_w 20600 g/mol was chosen as the carrier for application on the mucosa. DSC results indicated the transformation of a crystalline form of the drug into an amorphous form molecularly dispersed in the polymer.

Drug can be incorporated into branched polyester by two different approaches – by dissolving and by plasticization. Four solvents (2-butanone, dichlormethane, ethyl acetate, methyl formate) were tested. Methyl formate was evaluated as the most appropriate since it exhibits high volatility, high vapour pressure, low viscosity and low surface tension. For these properties it is commonly used as a component of solvent systems to achieve quick drying coating finishes and in spray applications.

Plasticization is another way of how to ease incorporation of drug into branched polyester. Five plasticizers from the class of biodegradable esters with limited miscibility with water were chosen. Surprisingly, the less effective plasticizer was triethyl citrate which is one of the most often used plasticizers in pharmacy. Triacetin, ethyl salicylate and methyl salicylate showed medium efficiency. The most effective plasticizer was non-conventional ethyl pyruvate and therefore it was chosen for our study. Other advantages of ethyl pyruvate are low viscosity, good miscibility in water and polyester carrier, and also its therapeutic effect[3)].

It has been shown that plasticized systems behave as Newtonian liquids with constant viscosity. This means that the viscosity of the system can be set to a desired value by choosing certain plasticizer concentration and

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that this value is not influenced by share rate/stress during technological processing and application. Such behaviour is beneficial from both technological and application points of view.

We have presented remarkable mucoadhesive properties of branched polyesters in our previous papers[4]. The mechanism of mucoadhesion can be explained by good spreading and causing of intimate contact on the site of application, and by development of attractive forces between hydroxyl and carboxyl groups of the branched polyester. The adhesive force of plasticized systems was significantly influenced by the plasticizer concentration. The presence of 5% drug did not significantly influence the adhesive force.

The amount of drug released was assessed by HPLC, because spectrophotometric evaluation interfered by the presence of ethyl pyruvate. It can be seen that the rate of drug release significantly increases with the plasticizer concentration. Attractive interactions between the drug and carrier molecules arise when the plasticizer concentration is low or there is no plasticizer at all. Poor burst effect is influenced partly by low degree of swelling of branched polyester, partly by low initial concentration of polyester carboxyl groups. With prolonged influence of water medium, another carboxyl groups with the affinity to the drug are generated by hydrolytic process in the polyester carrier. Strongly hydrophilic character of water-soluble low molecular products of branched polyester degradation facilitates the dissolution and release in this way. The plasticizing effect of ethyl pyruvate increases with its concentration. This is caused by the increasing distance between individual molecules of the polyester carrier[5] which leads to a decrease in dipole-dipole interactions between the carrier and drug. This effect was observed at plasticizer concentrations of 30% and more.

Conclusions

We developed a biodegradable polymeric mucoadhesive system based on the solid molecular dispersion of drug and branched poly(lactic-co-glycolic) acid branched on tripentaerythritol. The drug incorporation into the polyester was carried out either by dissolution of both components in methyl formate followed by its evaporation, or by plasticization using different plasticizers. The polymeric system formulated by our team offers several benefits: 1. increased solubility of molecularly dispersed drug in amorphous polymer, 2. excellent adhesion to hydrophilic surfaces thanks to mucoadhesive properties of branched polyester carrier, due to the attractive interactions between a drug and branched polyester, 3. prolonged drug release, 4. supportive healing and anti-inflammatory effects given by the presence of ethyl pyruvate as a multifunctional plasticizer, 5. possibility to adjust the consistency of the matrix to fit different methods of application (sticking, smearing, spraying) by changing plasticizer concentration.

Conflicts of interest: none.

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