

Controlled release formulations using polymer-based dry powders for pulmonary drug delivery

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Summary

Our aim was to develop controlled release dry powder formulations for inhalable drugs. We chose poly(lactic-co-glycolic acid) - poly(ethylene glycol)-block-co polymer (PLGA-*b*-PEG) types in order to control the release rate of salbutamol sulphate (Sbs) from a dry powder formulation. Polymer/Sbs-emulsions were spray dried resulting in microparticles with a fine particle fraction between 25 and 40 %. The drug dissolution profiles were investigated using a *in vitro* test system. A sustained release of Sbs was achieved over up to 24 hours. Polymers containing glycolide led to a faster drug release. The lowest drug burst release and the longest sustained release profile was reached using an poly lactide - poly(ethylene glycol) - poly lactide-triblock-co-polymer. The resulting formulation was then tested *in vivo* using the guinea pig Konzett Rößler-model. Bronchospasms were induced by intravenous injections of acetylcholine (Ach). Compared to inhaled Sbs-solution the polymer/Sbs-microparticles showed a significant bronchoprotection even after 18 hours following powder inhalation. These results demonstrate that a significantly prolonged therapeutic effect can be achieved in the lung following inhalation of a controlled release dry powder formulation.

Introduction

The development of controlled release formulations for inhalable drugs has been widely investigated since several years. Nonetheless, no controlled release product for pulmonary application is currently on the market. The reduction of the dosing frequency is of great concern for a number of pulmonary disorders including asthma and chronic obstructive pulmonary disease (COPD). In particular, short-acting β_2 -adrenergic receptor agonists used for the relief of asthma- and COPD-related bronchospasms have a relatively short plasma half life that constrain the patient to an administration of the drug every 4-6 hours. A controlled release formulation leading to a prolonged duration of action of more than 8 hours would prevent nocturnal exacerbation in bronchial asthma. Controlled release formulations are widely used in oral or parenteral formulations but have not been established for pulmonary applications. Current research approaches include the use of liposomes, micro- and nanosuspensions and dry powder formulations. Liposomes have been widely investigated but suffer from a poor physical stability during the nebulization process. To date, the commercial use of such products is thus difficult. For similar reasons it is also difficult to aerosolize a particle suspension in a way to ensure a constant delivered dose to the lung. Therefore, dry powder formulations have attracted attention. The formulation typically contains structural components of the particle as well as agents allowing the release of the drug over an extended period of time. These include lipids, proteins, sugars or synthetic polymers such as poly(vinyl alcohol) or polyesters. In particular, PLGA has been widely used, as it is considered biodegradable and weakly toxic. Both hydrophobic and hydrophilic drugs can be encapsulated and it has been used in parenteral controlled release formulations for many years. In addition to the biocompatibility and the controlled release property a dry powder formulation needs to satisfy other critical requirements. These include an aerodynamic particle size of 1-5 μm and the ability to generate a fine particle fraction of at least 30% using a commercially available dry powder inhaler. The aim of this work was to prepare PLGA-based controlled release dry powder formulations using salbutamol sulphate as a hydrophilic model drug substance. In order to provide a hydrophilic reservoir in the polymer matrix the polymer was modified by PEG. Polymers with diblock (A-B) or triblock (A-B-A) structures were tested.

Materials and Methods

The following PLGA / PLA / PEG block co-polymers (Boehringer Ingelheim) were chosen in order to assess the effect of the chemical composition, the polymer block-structure and the molecular weight of the polymer on the drug release property of the resulting particles:

1. LGPt8546: PLGA-*b*-PEG-*b*-PLGA (85% L-lactide, 15% glycolide, 4% PEG, 150 kDa)
2. LPt52: PLA-*b*-PEG-*b*-PLA (100% L-lactide, 5% PEG, 40 kDa)
3. LGPt5046: PLGA-*b*-PEG-*b*-PLGA (50% L-lactide, 50% glycolide, 4% PEG, 150 kDa)
4. LGPd8555: PLGA-*b*-PEG-*b*-PLGA (85% L-lactide, 15% glycolide, 5% PEG, 100 kDa)
5. LRPd7055: PLA-*b*-PEG-*b*-PLA (85% L-lactide, 15% D-lactide, 5% PEG, 100 kDa)
6. RGPd5055: PLGA-*b*-PEG-*b*-PLGA (50% D,L-lactide, 50% glycolide, 5% PEG, 100 kDa)

W/o-emulsions using dichloromethane as the organic phase were prepared by sonicating 100 ml water containing 750 mg salbutamol sulphate together with 400 ml of 0.75 % polymer solution. Polymers containing more than 4 % of PEG generated emulsions that were stable for more than 1 hour.

Spray drying was performed using a Büchi Mini Spray Dryer B-290 at an outlet temperature of 40-50 °C. The dry powder was collected through a high performance cyclone and the mass median aerodynamic diameter (MMAD) was controlled by a Sympatec Helos Laser Diffractionmeter equipped with a Rodos dispersing unit. Particles with a X_{50} between 1 and 5 μm were further investigated. The aerodynamic particle size distribution (aPSD) was determined using an Anderson Cascade Impactor (ACI, Copley Scientific). The dry powder was delivered into the

ACI using a HandiHaler® (Boehringer Ingelheim) containing a PE-capsule loaded with 10 mg powder and triggered during 6.15 sec at 39 L/min.

The dissolution profiles were assessed using an *in vitro* test system based on a Franz diffusion cell connected to an UV/Vis-Spectrometer (Lambda 35, Perkin Elmer). The Sbs concentration was measured at 225 nm. The dissolution media was PBS buffer maintained at 37 °C. In order to investigate the fine particle fraction a cellulose membrane (RC 55, Whatman) was placed onto the Stage F (Filter) of an ACI containing stages 0 and 1 only. The ACI was run as for the determination of the aPSD.

To assess the controlled release properties *in vivo* a therapeutic animal protocol based on the Konzett-Rössler model was developed. Ach-solutions were intravenously injected into anesthetized guinea pigs every 10 min at increasing concentrations, from 2 to 20 µg/kg. Bronchospasms were determined by overflow measurements according to the Konzett-Rössler model. The formulations containing 300 µg/kg Sbs were delivered up to 18 hours before the Ach-treatment. Sbs-solution used as control was inhaled using the RespiMat® nebulizer connected to the animal's trachea. Controlled release formulations were delivered using an experimental small animal dry powder inhalation system (Activaero).

Results and discussion

Particle preparation

Salbutamol sulphate/polymer particles were generated by spray drying a w/o-emulsion in which the drug was dissolved in the aqueous phase. Figure 1 shows the aerodynamic particle size distribution (a) and the morphology by scanning electron microscopy (b) of particles containing the LGPt8546 polymer as an example. The fine particle fraction as calculated from the ACI experiment was 30.7 % using this polymer. The morphology showed an irregular structure that is typically found with particles spray dried from an emulsion.

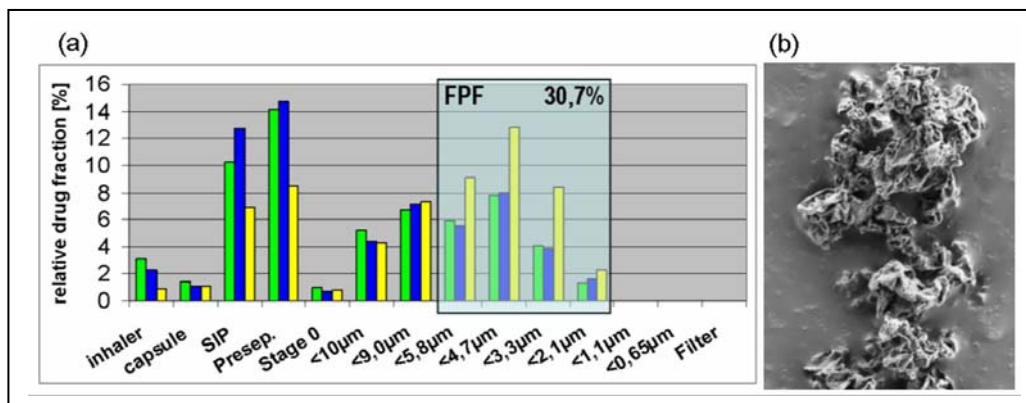


Figure 1. Aerodynamic particle size distribution (a) and a morphology (b) of spray dried salbutamol sulphate/polymer particles.

Similar particles could be generated using the polymers described above. Polymers with a PEG content of 10 % or more were tested as well, but had a glass transition temperature below room temperature and could not be spray dried using the Büchi spray dryer. In addition, polymers with molecular weights of 600 kDa or more displayed a viscosity in DCM that did not allow the generation of particulate materials (not shown). Since the polymers were not water soluble the encapsulation of Sbs required the generation of an emulsion, which could be achieved due to the emulsifying properties of the PLGA-*b*-PEG polymers.

Drug dissolution profile *in vitro*

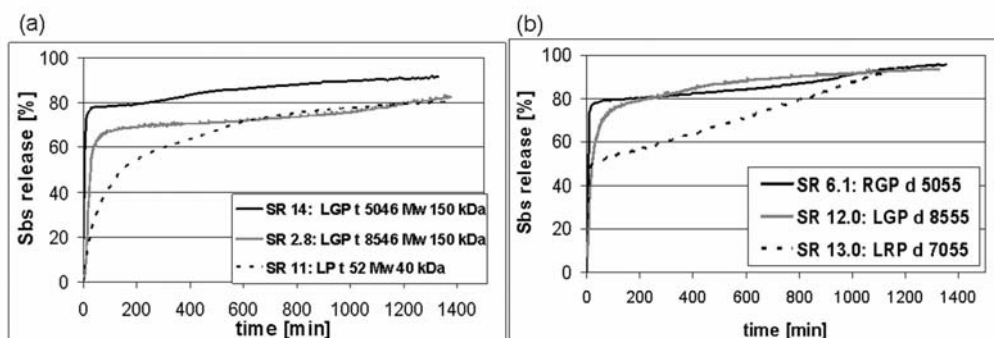


Figure 2. Drug dissolution profile from the fine particle fraction of Sbs/polymer particles. Influence of the polymer chemical composition on the dissolution profile using a triblock (a) - or diblock (b) co-polymer structure.

The controlled release properties of the spray dried particles were assessed using an *in vitro* test system. This system allows the investigation of the fine particle fraction. As shown in Figure 2 a retarded release could be obtained with some of the tested polymer types. Moreover, the chemical composition of the polymer influenced the drug release profile. Using polymers with both a triblock (a) – or a diblock (b) structure a more prolonged release profile was obtained with less glycolide, respectively with a higher lactide content. PEG-content, molecular weight or the molecular structure had only a slight influence on the dissolution profile (not shown).

Animal studies

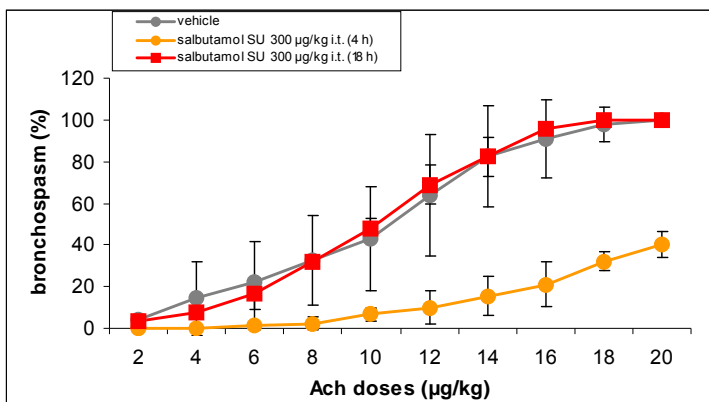


Figure 3. Duration of action of Sbs inhaled as a liquid aerosol formulation in the Konzett-Rößler animal model.

Controlled release formulations were tested *in vivo* on a bronchoconstriction therapeutic animal model. In this model bronchospasms are induced following i.v. injections of Ach (Figure 3, grey line). Increasing percentages of bronchospasms are observed with administration of increasing doses of Ach. However, if 300 µg/kg Sbs were inhaled as a liquid aerosol formulation bronchospasms were reduced 4 hours post dose (Figure 3, orange line). At 18 hours post dose, no significant bronchoprotective effect was found (Figure 3, red line).

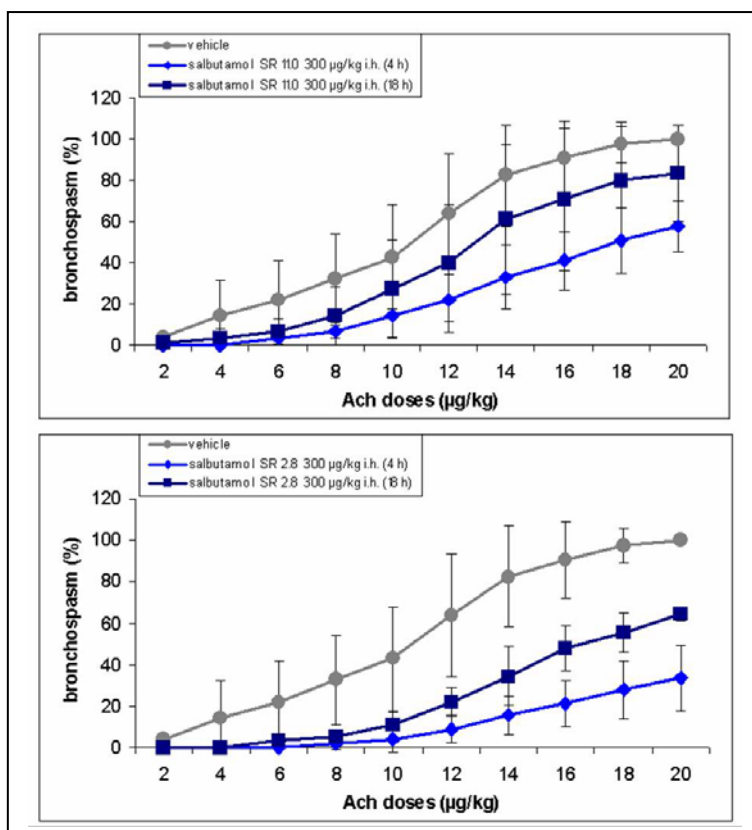


Figure 4. Bronchoprotective effect of Sbs-controlled release formulations *in vivo* following dry powder inhalation. SR11 particles containing the LPT52 polymer (top) and SR2.8 particles containing the LGPt8546 polymer (bottom).

Since the triblock-co-polymer LPT52 showed a dissolution profile with the lowest drug burst release and the most sustained controlled release (SR11-particle in Figure 2a) it was tested in the animal studies. Following delivery using a powder dispersion and inhalation device for small animals a strong bronchoprotective effect was also observed after 4 hours. In contrast to the Sbs solution a significant effect was still observed after 18 hours demonstrating a prolonged therapeutic effect *in vivo* (Figure 4, top). SR2.8 particles containing the LGPt8546 triblock co-polymer also showed a retarded release behaviour *in vitro* (Figure 2a), and were also tested *in vivo* (Figure 4, bottom). Also in this case bronchoprotection was observed both at 4 and 18 hours following dry powder inhalation. The bronchoprotective effect was slightly more pronounced as compared to the SR11-particles. Additional experiments at later time points will be necessary to confirm that the duration of action could be longer with the SR11-particles.

Conclusion

PL(G)A-*b*-PEG-*b*-PL(G)A and PLGA-*b*-PEG co-polymers have been shown to provide a means to generate controlled release dry powder formulations for inhalable drugs. In particular, a water soluble drug can be encapsulated without an additional emulsifier. The controlled release profile can be tuned through the chemical composition of the polymer and influences also the duration of action of the drug in the therapeutic animal model. This provides the opportunity to gain a better control of disease states through an appropriate design of the polymer excipient.