Novel Surface Modified PLGA Microspheres to Modulate Drug Release Kinetics

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Introduction
Drug delivery systems (DDS) have been designed to alter the pharmacokinetics (PK) and biodistribution (BD), or to function as drug reservoirs. Poly (lactic-co-glycolic acid) (PLGA) microspheres have been studied a lot as a promising drug delivery device because of the biocompatibility and biodegradability of PLGA as well as the convenient fabrication and administration of microspheres. However, zero order release is still a challenge for such devices due to the complicated drug release mechanisms which result in biphasic or triphasic release profiles accompanied by an initial burst. Physically or chemically modified PLGA microspheres have attracted more and more interests because of the possibility of controlling the drug release characteristics by a molecular fence effect or by a two stage release mechanism. To the best of our knowledge, PLGA microspheres modified with a surface modification layer of chitosan by a controlled surface modification method was not studied and the in vitro release kinetics of such device was not known. In this study, a surface modification layer of chitosan was successfully covalently bonded to rifampicin loaded PLGA microspheres by a controlled surface modification method and the drug release rate was modulated by the modification layer to achieve a near zero order release kinetics.

Methods
All the reagents were obtained from Sigma-Aldrich unless otherwise specified. Chitosan (75-85% deacetylated) was dissolved in acetic acid and purified by filtration before use. Other reagents were used as received.

PLGA microspheres loaded with rifampicin were fabricated with two types of PLGA (76-115kD, 75:25 and 7-17kD, 50:50) in order to modulate the degradation rate of PLGA. Briefly, 50mg PLGA A (75:25) and 50mg PLGA B (50:50) were dissolved in 1mL dichloromethane. 10mg rifampicin was added to PLGA solution and shaken until completely dissolved. Rifampicin loaded PLGA microspheres were obtained by emulsifying the mixture in 8mL deionized water containing 1% (w/v) poly (vinyl alcohol) on a vortex at max speed for 1 minute, followed by stirring at room temperature for 12h at 400rpm to remove dichloromethane. For comparison, rifampicin loaded microspheres were also fabricated with only PLGA A. Surface modification layer of chitosan was coupled to PLGA microspheres by a controlled surface modification method. PLGA microspheres were hydrolyzed in sodium hydroxide solution with a certain concentration for a certain period to create surface carboxyl groups. Chitosan was then coupled to PLGA microspheres by carbodiimide chemistry. Unreacted chitosan was washed away by acetic acid. The resultants were treated in 2mL 6% glutaraldehyde for 1h to crosslink chitosan. Fabrication was repeated to obtain enough samples for characterization.

PLGA microspheres were characterized by SEM, microscopy and FTIR. In vitro release characteristic of original and surface modified microspheres were tested according to a described method [1] with small modifications.

Results Section
Microscopy and SEM images are shown in Figure 1. Yellow color was imparted to microspheres by rifampicin (Fig. 1(a)). SEM image indicated that PLGA microspheres were spherical and the surface was smooth.

Figure 1. Microscopy image of rifampicin loaded PLGA microspheres (a) and SEM image of rifampicin loaded PLGA microspheres (b).

In vitro release of surface modified PLGA (A) microspheres exhibited reduced initial burst and more uniform release rate compared with unmodified PLGA (A) microspheres. However, no release was detected after day 13 which may be due to the relatively slow degradation rate of PLGA 75:25. On the other hand, PLGA 75:25 mixed with PLGA 50:50 showed sustained releases over the whole testing period. PLGA 50:50 has much faster degradation rate compared with PLGA 75:25 so that the overall degradation rate can be modulated and the lag phase was avoided. However, unmodifiedPLGA (A-B) microspheres showed a significant burst release at day 10 which is due to the degradation of PLGA 50:50. It was found that this burst release can be reduced by surface modification with chitosan so that more uniform release of rifampicin was obtained.

Discussion
By a controlled surface modification method, a surface modification layer of chitosan can be covalently bonded to PLGA microspheres. The coupling of chitosan was proved by FTIR and microscopy image. Surface modified PLGA (A-B) microspheres showed reduced burst release and near zero order in vitro release profile which suggest the drug release characteristic modulation effect of the surface modification layer. Further studies are needed to verify the mechanisms for modulating the in vitro release characteristics of rifampicin.

Significance
This work provided a controlled surface modification method for PLGA microspheres by which a surface modification layer of chitosan can be covalently bonded to PLGA microspheres in a meticulous manner. Furthermore, it was found that the release characteristics of rifampicin can be modulated by chitosan surface modification layer and a near zero order in vitro release kinetics was achieved.

References

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