Supplementary Information for

Sequential controlled-released dual-drug loaded scaffold for guided bone regeneration in a rat fenestration defect model

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Supplementary information(SI)

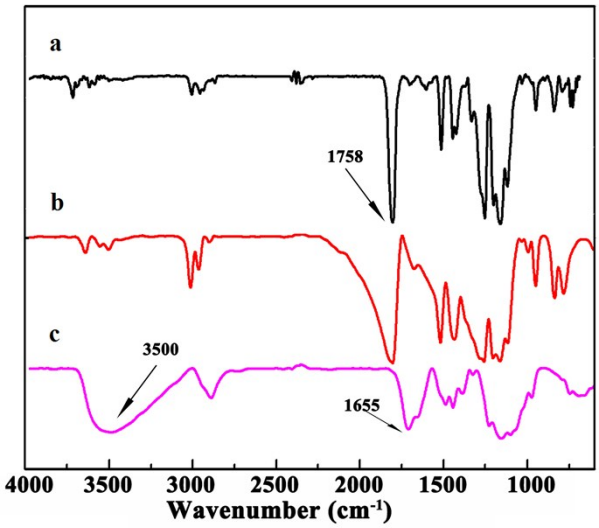

Figure S1. FT-IR spectra of pure PLLA (a), DDDS(b) and CSMs (c)

Figure S1b shows the distinct FTIR spectra of the DDDS from the pure PLLA and CSMs (Figure S1a and S1c, respectively). The amino band of 1655 cm^{-1} in the CSM shifted to 1650 cm^{-1} in the DDDS, while an original strong band of the PLLA component at 1758 cm^{-1} for the ester group becomes significantly weaker and markedly wider. The intensity of the stretching bands overlapped and centered near 3500 cm^{-1} for the hydroxyl and amino groups pronouncedly decreases. All of these events indicated that there were obvious interactions among the amino, carboxyl, and hydroxyl groups of PLLA and chitosan. Similar results were also previously reported by Chen et al.[1] and Niu et al.[2].

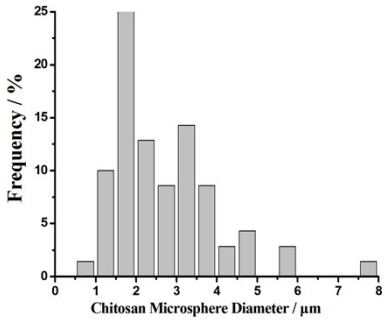

Figure S2. Chitosan microsphere size distribution

The chitosan microspheres size distribution is shown in Figure S2. As could be seen from the results, the CSMs particle size is in the range of 2-8 μm. Moreover, the average diameter of microspheres is 2.65 μm.

To study the kinetic mechanism of drug release, four models were fitted: zero order, first order, Higuchi's model and Korsmeyer-Peppas model.[3] These models are given in the following equations:

$$\text{Zero order: } Q_t = Q_0 + K_0 t$$
$$\text{First order: } \ln Q_t = \ln Q_0 + K_1 t$$
$$\text{Hugichi's model: } Q_t = K_H \sqrt{t}$$
$$\text{Korsmeyer} - \text{Peppas model: } M_t / M_\infty = kt^n$$

where Q_0 is the initial amount of drug in solution (it is usually zero) and Q_t is the amount of drug released in time t; K_0, K_1 and K_H are the zero-order, the first-order release constant and the Higuchi dissolution constant respectively, and M_t/M_∞ is the fraction of drug released at time t. k is the rate constant, and n is the release exponent of the Korsmeyer-Peppas model.

The release kinetics parameters for the four formulations based on the *in vitro* release profiles are presented in Table S1. It could be observed that the *in vitro* release of both drugs followed the Korsmeyer-Peppas release kinetic model with a highest value of R^2 (correlation coefficient) value. Moreover, the n (release exponents) were found to be between 0.16 (for NRG from NRG-PTL-PLLA) and 0.44 (for NRG from DDDS), respectively.

Table S1 Release kinetic parameters calculated from the drug release data by different mathematical models (R^2=correlation coefficient; n= release exponent, indicative of the type of transport).

sample	Zero order R^2	First order R^2	Hugichi's model R^2	Korsmeyer-Peppas

				model	
				R^2	n
NRG from NRG-PTL-PLLA	0.325	0.736	0.597	0.874	0.16
PTL from NRG-PTL-PLLA	0.599	0.814	0.754	0.943	0.28
NRG from DDDS	0.817	0.908	0.969	0.976	0.44
PTL from DDDS	0.541	0.798	0.706	0.917	0.27

Reference

[1] C. Chen, L. Dong, M. K. Cheung, *European Polymer Journal*, 2005, **41**, 958–966.

[2] X. Niu, Q. Feng, M. Wang, X. Guo, Q. Zheng, *Polymer Degradation and Stability,* 2009, **94**, 176-182.

[3] J. Siepmanna, N. A. Peppas, Adv. Drug Deliver. Rev., 2001, 48, 139-157.