Radiopaque and uniform alginate microspheres loaded with tantalum nanoparticles for real-time imaging during transcatheter arterial embolization

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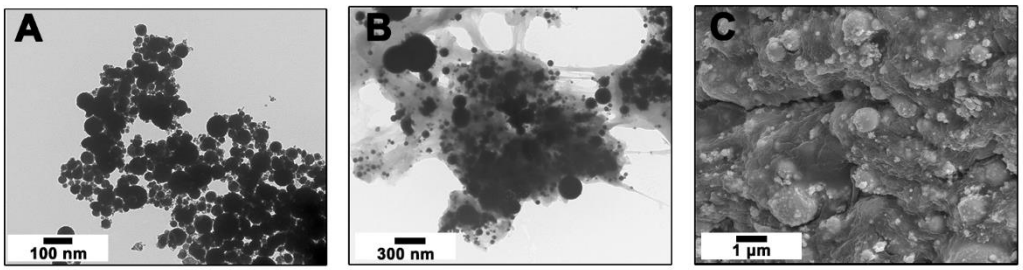

Figure S1. TEM micrographs of (A) Ta nanoparticles and (B) Ta@CaAlg microspheres; (C) SEM micrograph of the cross-section of Ta@CaAlg microspheres.

Ta NPs were not monodispersed, whose diameter ranged from 17 nm to 2 μm (Figure S1A). The average diameter tested by a photon correlation spectrometer (DLS, Zetasizer Nano ZS90, Malvern Instruments Ltd, UK) was 54 ± 24 nm. However, SEM and TEM micrographs of Ta@CaAlg microspheres show that Ta NPs dispersed homogenously through the microsphere.

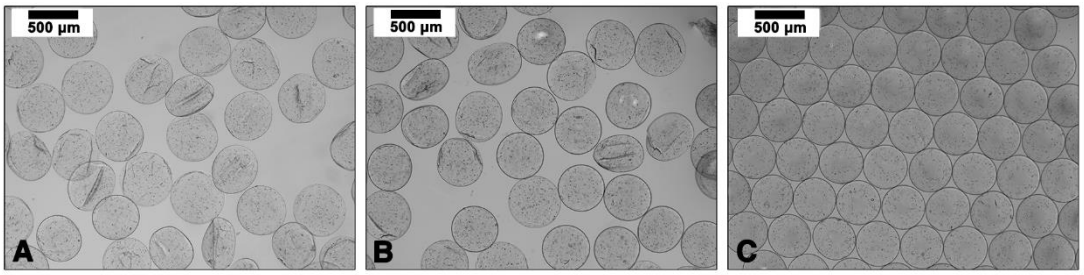

Figure S2. Optical micrographs of CaAlg microspheres prepared with different concentration of $CaCl_2$: (A) 0.2, (B) 0.4, and (C) 0.6 M. Operating parameters: size of spinneret = 25 Gauge; spinneret voltage = 10 kV.

The morphology of microspheres was related with the concentration of collecting solution. As shown in Figure S2, the microspheres were wrinkled and irregular when the concentration of $CaCl_2$ was low. As a result, the diameter deviations of microspheres produced with various $CaCl_2$ concentration were significantly different. Their diameters were 489 ± 64 μm, 476 ± 26 μm and 437 ± 14 μm, when $CaCl_2$ concentrations were 0.2, 0.4 and 0.6 M, respectively. The optimal concentration of $CaCl_2$ was 0.6 M, which was used in the other experiments. These results indicated that an appropriate crosslink degree between guluronate blocks (G blocks) of alginate chain by Ca^{2+} could produce spherical microspheres. It could avoid irregular shaped particles, which would affect the embolic performance.

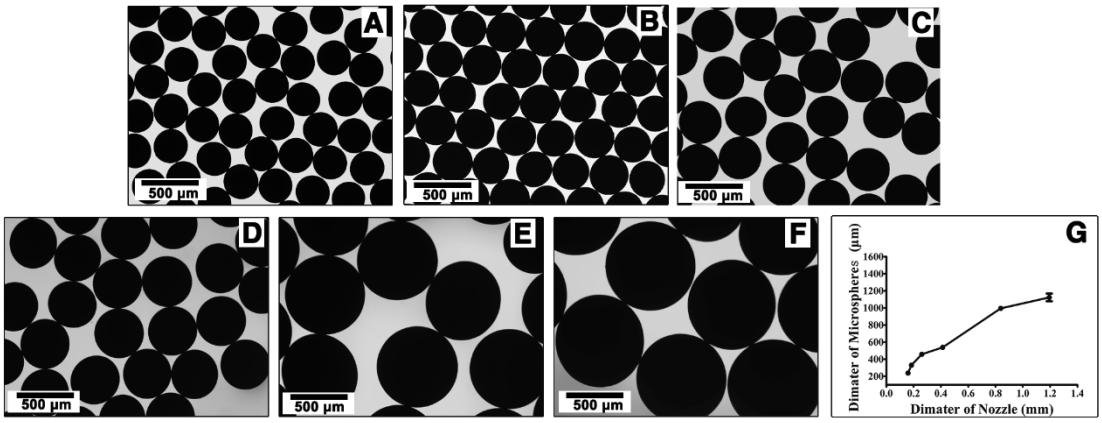

Figure S3. Optical micrographs of Ta@CaAlg microspheres prepared with different sizes of spinneret: (A) 30-Gauge (I.D.: 0.159 mm), (B) 28-Gauge (I.D.: 0.184 mm), (C) 25-Gauge (I.D.: 0.26 mm), (D) 22-Gauge (I.D.: 0.413 mm), (E) 18-Gauge (I.D.: 0.838 mm) and (F) 16-Gauge (I.D.: 1.194 mm). (G) Diameter distribution diagram of Ta@CaAlg microspheres on size of spinneret. Operating parameters: spinneret voltage = 10 kV.

For electrospraying, the size of spinneret is a key parameter to control the diameter of microspheres. Different sizes of monodispersed microspheres were obtained by varying the sizes of spinnerets, while the other parameters were maintained the same. The diameters of Ta@CaAlg microspheres were 1122 ± 45, 994 ± 30, 537 ± 12, 457 ± 11, 330 ± 5 and 258 ± 10 µm, when the spinneret sizes were 16, 18, 22, 25, 28 and 30 Gauge, respectively. These results showed that the size of spinneret had a major impact on the diameter of microspheres.

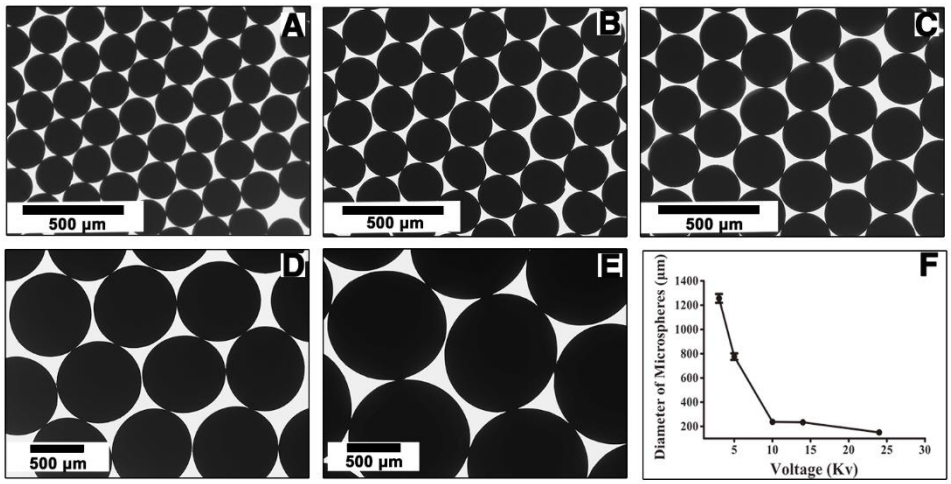

Figure S4. Optical micrographs of Ta@CaAlg microspheres prepared with different spinneret voltages: (A) 24, (B) 14, (C) 10, (D) 5 and (E) 3 kV. (F) Diameter distribution diagram of Ta@CaAlg microspheres on spinneret voltage. Operating parameters: size of spinneret = 30 Gauge.

Electric field is another key parameter, which is the motive force in electrospraying. As shown in Figure S4, when the spinneret voltage was the only variable, the diameter of Ta@CaAlg microspheres decreased with the increasing of the voltage. When the spinneret voltages increased from 3, 5, 10, 14, to 24 kV, the diameters of Ta@CaAlg decreased from 1256 ± 36, 775 ± 27, 258 ± 10, 234 ± 8, to 150 ± 5 μm. Thus, through adjusting spinneret size and voltage, monodispersed microspheres with a wide range of diameters can be achieved. It can meet the requirements of precisely calibrated embolics and flexible clinical applications.

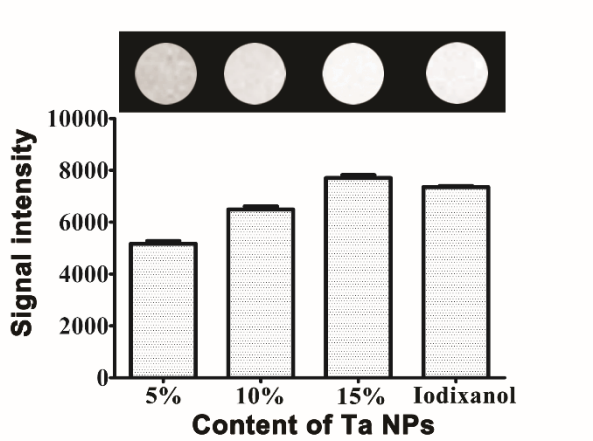

Figure S5. X-ray images and signal intensity of Ta@CaAlg microspheres fabricated with different concentration of Ta NPs. Iodixanol solution with a concentration of 300 mg I/mL was used as a reference.

The visibility of Ta@CaAlg microspheres and iodixanol solution under X-ray radiation was investigated by an IVIS Lumina XR system (Figure S5). The brightness of embolics in the blood vessel under X ray is an important indicator to the clinicians during TACE procedure. So the X-ray images and relative signal intensity of packed microspheres and iodixanol solution were tested, which were stored in the same vial with the same volume. When Ta NP concentrations were improved from 5%, 10%, to 15% (weight percentage of Ta to solution), the relative signal intensities acquired on IVIS Lumina XR imaging system increased from 5167, 6490, to 7706, respectively. The intensity of Iodixanol solution was 7355, whose concentration was normally used. These results showed that the X-ray imaging capability of Ta@CaAlg microspheres prepared with 10% Ta NPs was almost equivalent to that of the commercial Iodixanol

solution. Thus, this concentration was used in the other experiments. As a result, the X-ray imaging capability of Ta@CaAlg microspheres could be adjusted by the concentration of Ta NPs in electrosprayed solution.

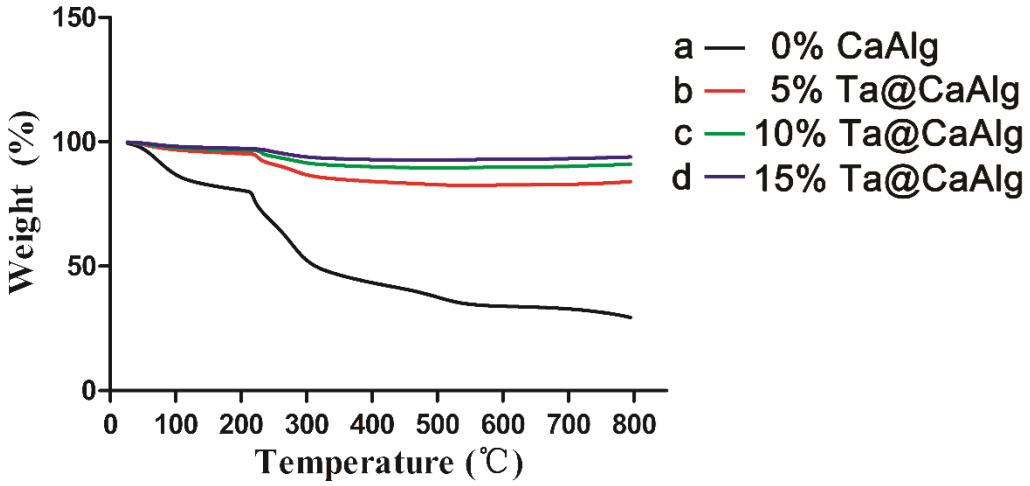

Figure S6. Thermogravimetric curves of Ta@CaAlg microspheres prepared with different concentrations of Ta NPs in electrosprayed solution: (a) 0%, (b) 5%, (c) 10% and (d) 15% (w/v).

The thermogravimetric analysis (TGA) of Ta@CaAlg microspheres showed that altering the content of Ta NPs in the electrosprayed solution could tune the percentage of Ta NPs in Ta@CaAlg microspheres leading to the differences of radiopacity. The residues of microspheres, with Ta NP content of 0%, 5%, 10% and 15% in the electrosprayed solution, were 29.41%, 84.01%, 91.04% and 93.91% (weight percentage) after calcination up to 800ºC, respectively (Figure S6). Meanwhile, Ta@CaAlg microspheres also presented excellent thermal stability below 220°C in comparison with that of CaAlg microspheres. It was owed to the existence of Ta NPs in the alginate matrix.

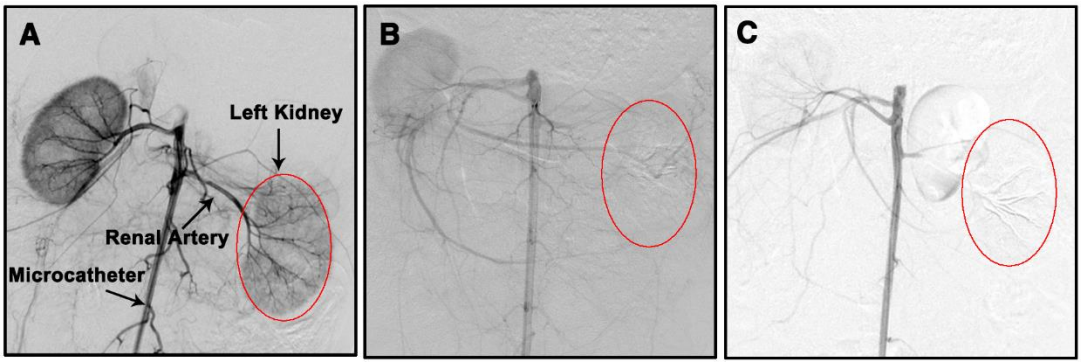

Figure S7. DSA images of left kidneys of rabbits (A) before, (B) immediately after and (C) 4 weeks after embolization by CaAlg microspheres.

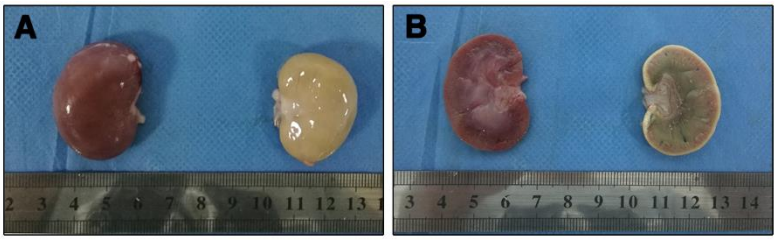

Figure S8. (A) Gross outside and (B) section views of normal (on the left) and embolized (on the right) kidneys with Ta@CaAlg microspheres after 4 weeks.

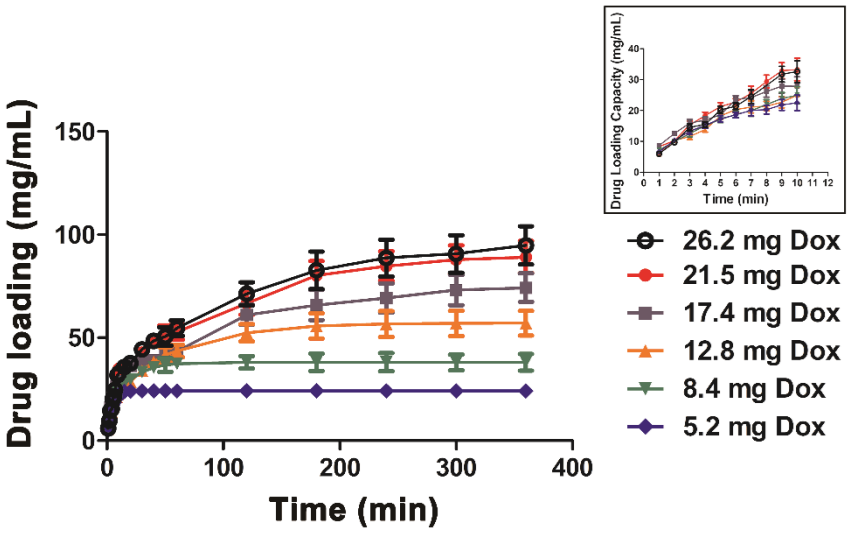

Figure S9. DL of Ta@CaAlg microspheres incubated in Dox solution with various initial Dox amounts at different time point. The figure inserted on the upper right was DL within the first ten minutes.