Shear-collapsible microscale aggregates of PLGA nanoparticles with the ability to target obstructed blood vessels

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BACKGROUND

Obstruction of critical blood vessels as in thrombosis and aterosclerosis is a leading cause of death and long-term adult disability worldwide. Effective treatment requires quick and invasive interventions through the systematic infusion of thrombolytic agents or the placement of a catheter in the affected vessel. Moreover, non-selective distribution of the thrombolytic drug increases bleeding risk. Blood vessels with luminal stenosis (narrowing) show a significant increase in fluid shear stress (>1000 dyne/cm2) compared to normal vessels (~70 dyne/cm2), a fact that can be exploited for targeting delivery to obstructed vessels.

OBJECTIVE

To prepare microscale aggregates of PLGA NPs with the ability to breakup under high shear stress into their forming NPs, which in turn adhere more effectively to the vessel surface compared with larger aggregates.

METHODS

Negatively and positively charged NPs were prepared based on poly(ethylene glycol) (PLGA) using an emulsion-solvent evaporation method. Nanoparticles surface charge was modulated by using carboxylic or amine species. Next, the microaggregates were prepared by mixing the negatively and positively charged NPs using a high-speed homogenizer. Optimized aggregates were achieved by controlling different parameters as: (i) composition of NPs; (ii) NPs ratio; or (iii) homogenization conditions (speed, duration). The produced NPs and aggregates were extensively characterized. To test the ability of the microaggregates to collapse under high shear stress, they were injected through a microchannel specially designed to mimics different vascular grading stenosis (low, medium, high). Furthermore, HUVEC cells were cultivated in the microfluidic system and labelled aggregates (Nile red-negative NPs and (FITC-positive NPs) were injected into the microchannel and observed under fluorescence microscope.

RESULTS

Particle size and zeta potential were 268.5 nm, -20.1mV and 179.2 nm, +20.9 mV for negative and positive NPs, respectively. The microaggregates had a globular shape and an average diameter of 6.8 µm. Aggregates passed through the microchannel contained ~30% of NPs as a result of aggregates collapse under the elevated shear. In addition, examination under fluorescence microscope provided another evidence for aggregates breakup.

CONCLUSION

The PLGA-based microaggregates show promise for targeted treatment of thrombosis, arteriosclerosis and thrombosis-associated disorders such as COVID 19 infection.

REFERENCES

[1] Korin N, et al. Science, 337(2012) 738-42.
[2] Berrocoso Domínguez E, et al. Nanomedicine, 13 (2017):2623-2632.

FIGURES

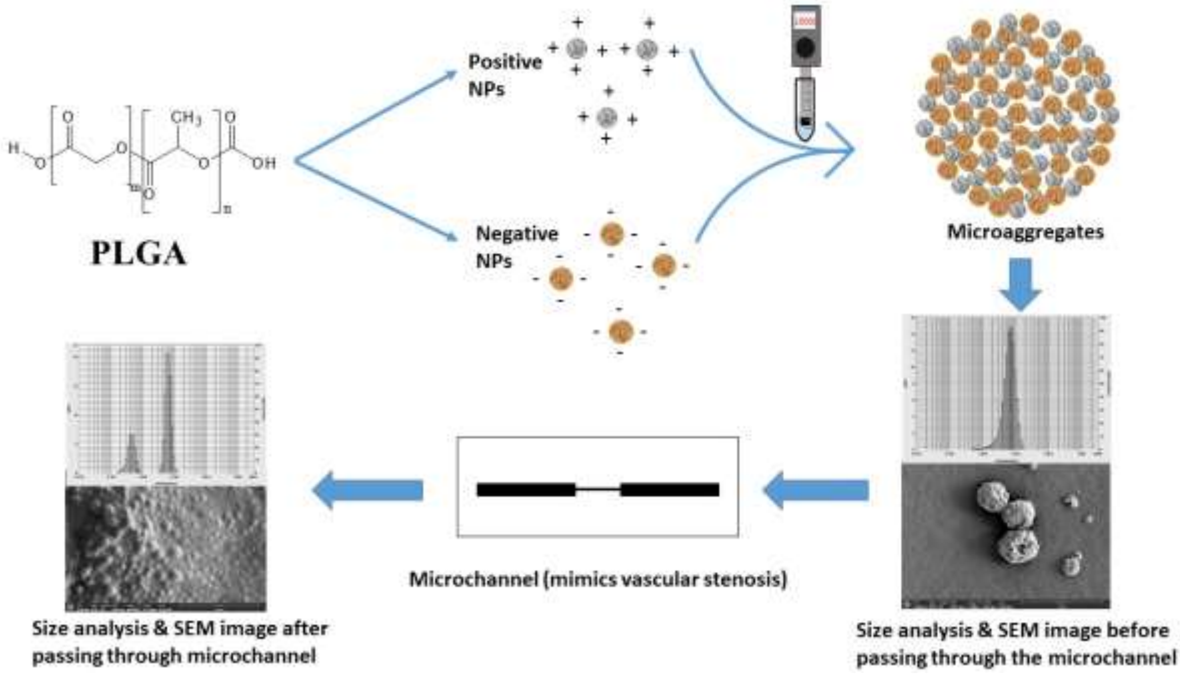

Figure 1: Synthesis of microscale aggregates with the ability to break up under high shear stress.