Osmotic Annealing Generates a Suite of Mechanically-Activated Microcapsules for Tunable Drug Delivery

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Introduction

- Musculoskeletal tissues experience loading patterns that can change with the onset of injury or disease and further intensify tissue damage [1-2].
- Drug delivery in response to the tissue's mechanical loading could provide on-demand biomolecule release when needed and lead to enhanced tissue repair.
- To that end, we developed mechanically-activated microcapsules (MAMCs) [3].

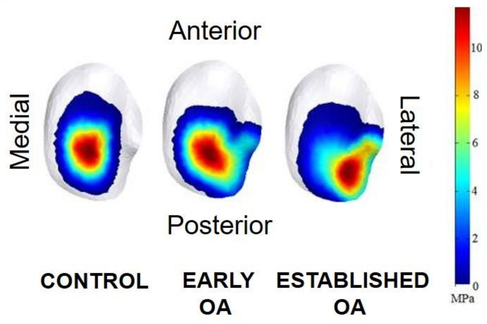
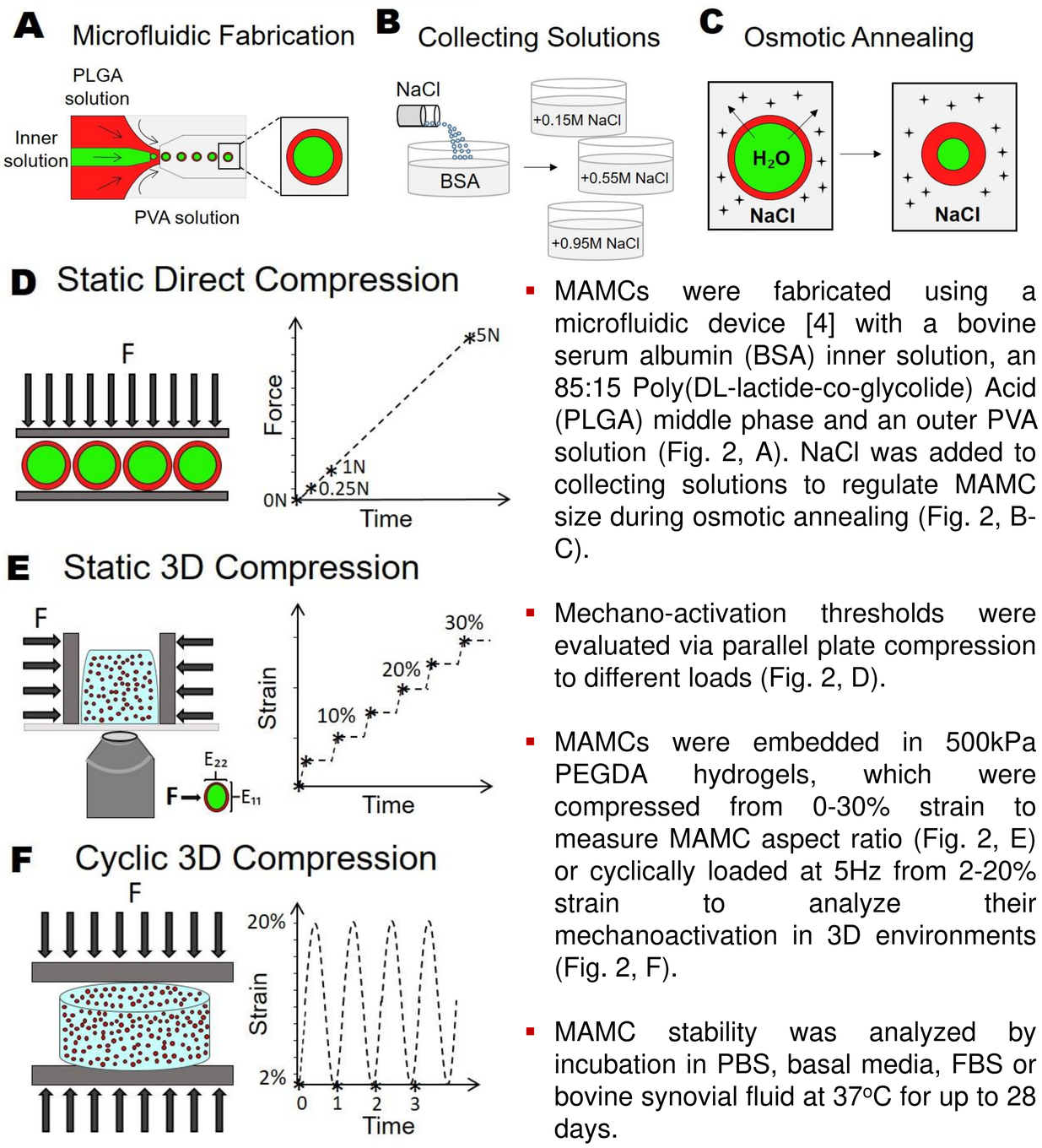


Figure 1. Contact pressure maps of human tibial plateau through progression of osteoarthritis (OA). Adapted from Meireles et al., 2017 [2].

This study aimed to develop MAMCs with different microcapsule size and shell thickness to generate MAMCs with different mechano-sensitivity and stability profiles.

Methods



- MAMCs were fabricated using a microfluidic device [4] with a bovine serum albumin (BSA) inner solution, an 85:15 Poly(DL-lactide-co-glycolide) Acid (PLGA) middle phase and an outer PVA solution (Fig. 2, A). NaCl was added to collecting solutions to regulate MAMC size during osmotic annealing (Fig. 2, B-C).
- Mechano-activation thresholds were evaluated via parallel plate compression to different loads (Fig. 2, D).
- MAMCs were embedded in 500kPa PEGDA hydrogels, which were compressed from 0-30% strain to measure MAMC aspect ratio (Fig. 2, E) or cyclically loaded at 5Hz from 2-20% strain to analyze their mechanoactivation in 3D environments (Fig. 2, F).
- MAMC stability was analyzed by incubation in PBS, basal media, FBS or bovine synovial fluid at 37°C for up to 28 days.

Figure 2. MAMCs were generated using a microfluidic device (**A**) and osmotically annealed using NaCl solutions (**B-C**). MAMCs were compressed between parallel plates to assess mechano-activation thresholds (**D**). MAMCs in hydrogels underwent static compression to assess MAMC deformation (**E**) or were cyclically compressed to assess resistance to rupture in 3D environments (**F**).

Results

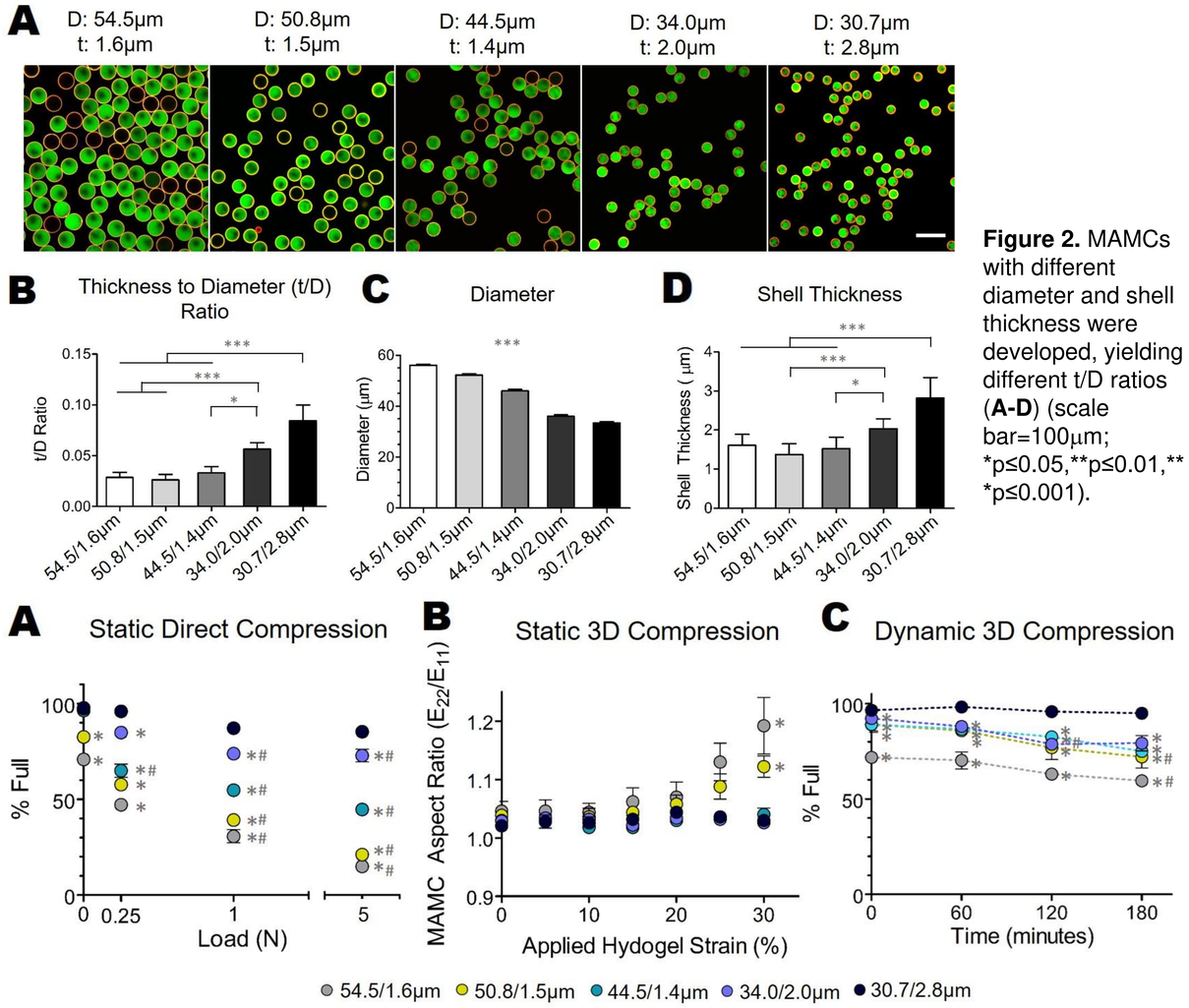


Figure 2. MAMCs with different diameter and shell thickness were developed, yielding different t/D ratios (**A-D**) (scale bar=100μm; *p≤0.05,**p≤0.01,***p≤0.001).

Figure 3. MAMCs with smaller diameter and larger shell thickness were more resistant to both static (**A-B**) and dynamic compression (**C**) (* p≤0.05 vs. 30.7/2.8μm, # p≤0.05 vs. 0 Load, Strain, or Minutes).

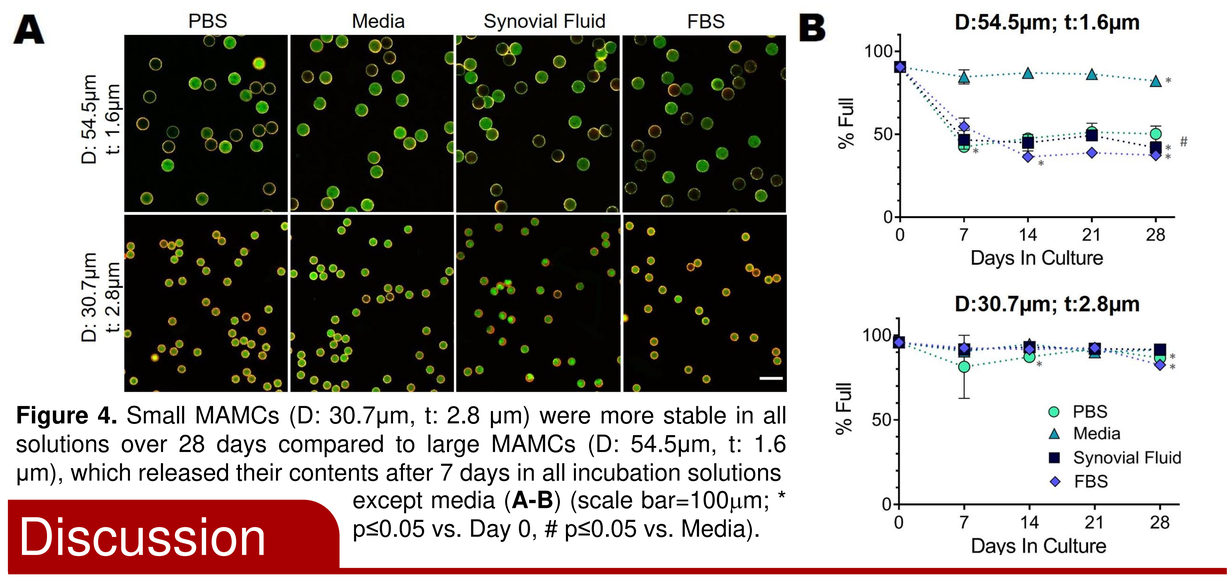


Figure 4. Small MAMCs (D: 30.7μm, t: 2.8 μm) were more stable in all solutions over 28 days compared to large MAMCs (D: 54.5μm, t: 1.6 μm), which released their contents after 7 days in all incubation solutions except media (**A-B**) (scale bar=100μm; * p≤0.05 vs. Day 0, # p≤0.05 vs. Media).

Discussion

- Osmotic annealing expanded the range of MAMC mechano-activation profiles, increased their resistance to static and dynamic compressive loads in 2D and 3D environments, and improved their stability *in vitro*.
- The wide suite of MAMCs developed in this study will allow for sequential on-demand delivery of molecules for musculoskeletal tissue regeneration.

References/Acknowledgements

[1] Sun+ *Ann NY Acad* Sci 2010, [2] Meireles+ *PLoS ONE* 2017, [3] Mohanraj+ *Adv Func Mat* 2019, [4] Tu+ *Langmuir* 2012

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