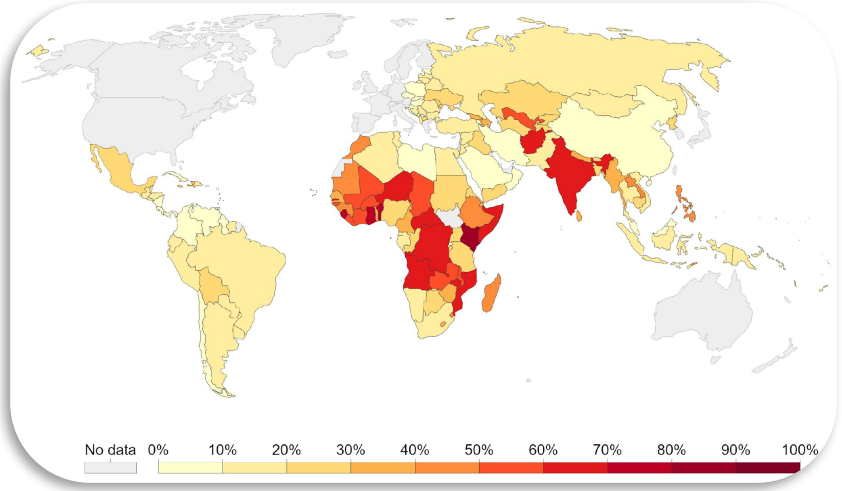
Poly(β-amino ester)-based microparticle platform for micronutrient stabilization and oral delivery

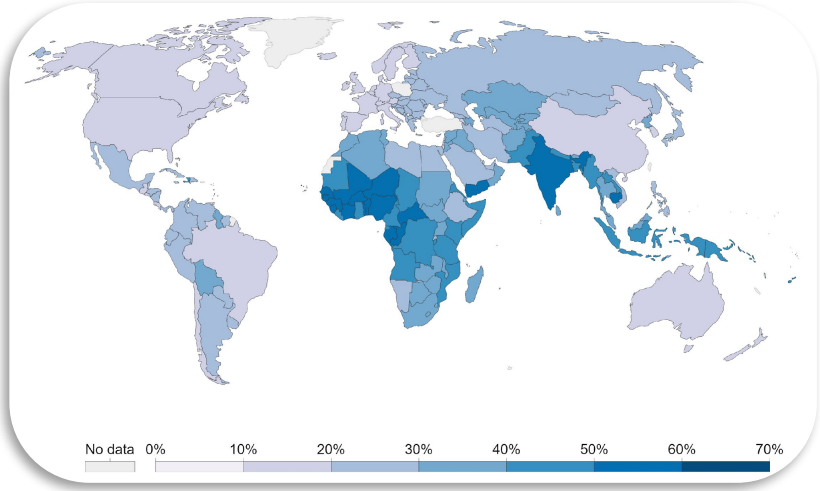
Linzixuan (Rhoda) Zhang
Chemical Engineering, MIT

CONTROLLED RELEASE SOCIETY
CRS 2023 ANNUAL MEETING & EXPOSITION
JULY 24-28, 2023 Paris Hotel » Las Vegas, NV, USA
THE FUTURE OF DELIVERY SCIENCE

Micronutrient deficiency is a global healthcare crisis in low-to-middle income countries



Vitamin A deficiency



Anemia

- **372 million** preschool-aged children and **1.2 billion** non-pregnant women of reproductive age are suffering from micronutrient deficiency globally
- **Vitamin A deficiency and anemia (deficiency of iron)** are two of the most severe micronutrient deficiencies

Black, et al., *The Lancet*, **2013**
Bailey, et al., *Annals of Nutrition and Metabolism*, **2015**
Stevens, et al., *The Lancet Global Health*, **2022**
https://ourworldindata.org/micronutrient-deficiency

Food fortification is an effective strategy to combat global micronutrient deficiency crisis

Food fortification:

A practice of improving commonly consumed foods with nutritional value by addition of essential vitamins and minerals

Advantages

- Cost effective
- Highly sustainable
- Widely applicable
- Successful examples

Olson, et al., *Nutrients*, **2021**

Food fortification is an effective strategy to combat global micronutrient deficiency crisis

Food fortification:

A practice of improving commonly consumed foods with nutritional value by addition of essential vitamins and minerals

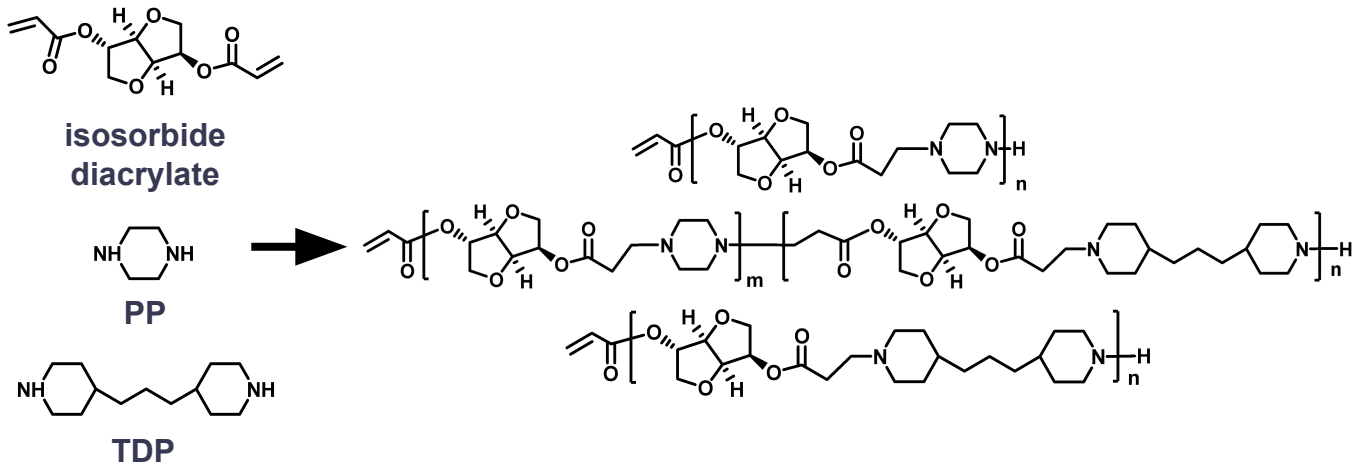
Challenges

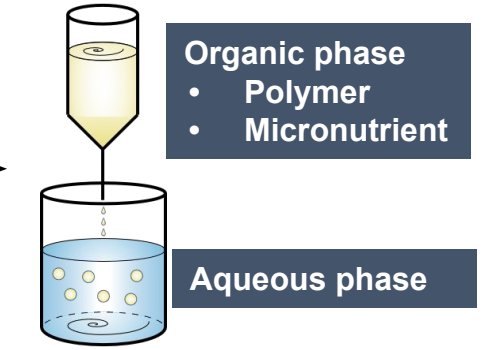
Stabilization	• Cooking conditions • Household storage conditions
Absorption	• Release after oral consumption • Bioavailability in digestive system

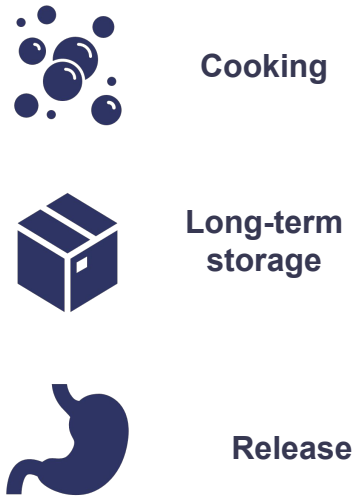
Olson, et al., *Nutrients*, **2021**

Poly(β-amino ester)-based microparticle platform for micronutrient stabilization and oral delivery

Synthesis of poly(β-amino ester) (PAE) → Fabrication of microparticles (MP) with micronutrient encapsulation → Characterization of micronutrient stabilization and release



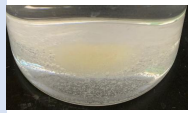




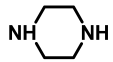
Lynn , et al. *JACS*, **2000**
TDP: 4,4′-trimethylenedipiperidine
PP: piperazine

The best candidate composition was selected based on MP fabrication results and VA protection efficacy

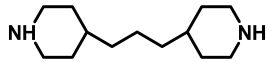
Label	TDP:PP Feed Ratio	MP Formation
PAE_A	0:100	No
PAE_B	25:75	No
PAE_C	50:50	**Yes**
PAE_D	75:25	**Yes**
PAE_E	**100:0**	**Yes**



Stevens, et al., *The Lancet Global Health*, **2022**
Sauvant, et al., *Food Research International*, **2012**
Runge, et al., *J. Agric. Food Chem.*, **2000**
Van den Broeck, et al., *J. Agric. Food Chem.*, **1998**



PP

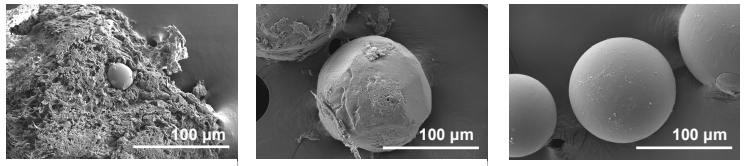


TDP

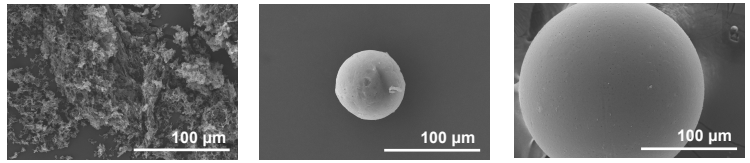
VA was used as a model micronutrient

- VA is sensitive to heat and light
- VA deficiency is globally prevalent
- VA deficiency is a leading cause of preventable childhood blindness

PAE_C **PAE_D** **PAE_E**



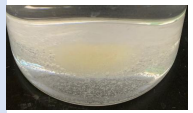
PAE MP



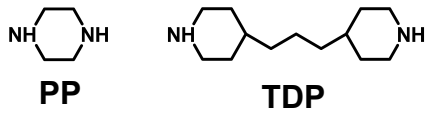
PAE MP with VA

The best candidate composition was selected based on MP fabrication results and VA protection efficacy

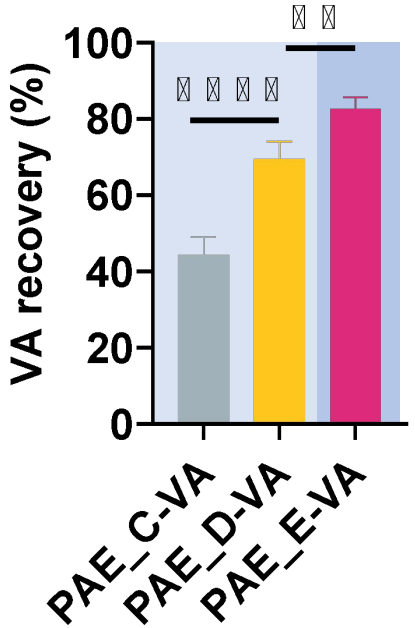
Label	TDP:PP Feed Ratio	MP Formation
PAE_A	0:100	No
PAE_B	25:75	No
PAE_C	50:50	**Yes**
PAE_D	75:25	**Yes**
PAE_E	**100:0**	**Yes**



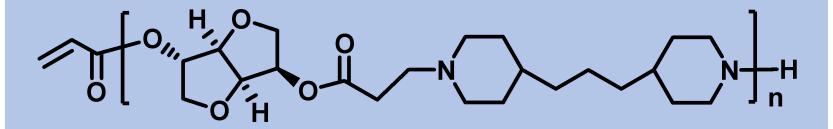
Stevens, et al., *The Lancet Global Health*, **2022**
Sauvant, et al., *Food Research International*, **2012**
Runge, et al., *J. Agric. Food Chem.*, **2000**
Van den Broeck, et al., *J. Agric. Food Chem.*, **1998**



VA recovery after 2-hour boiling in water

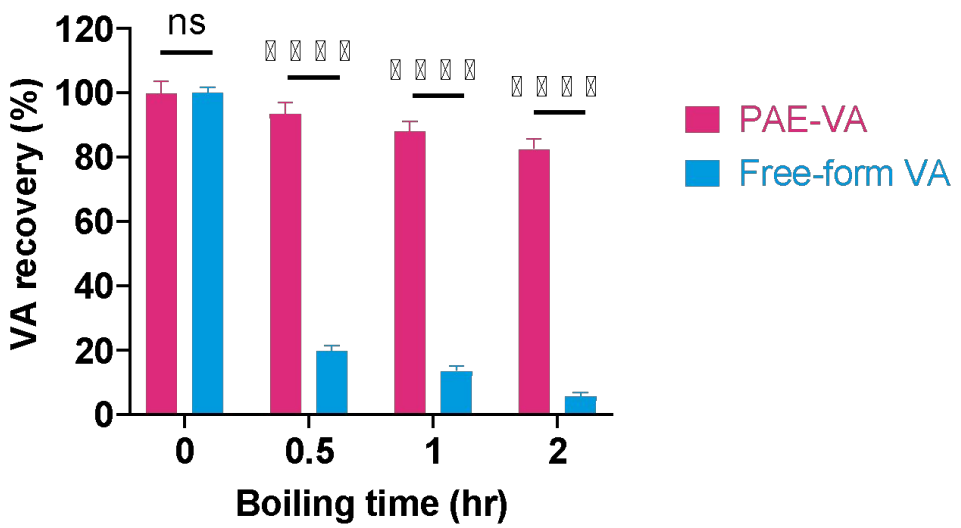


PAE_E* selected as the best candidate



PAE MPs presented robust protection for VA in simulated cooking condition

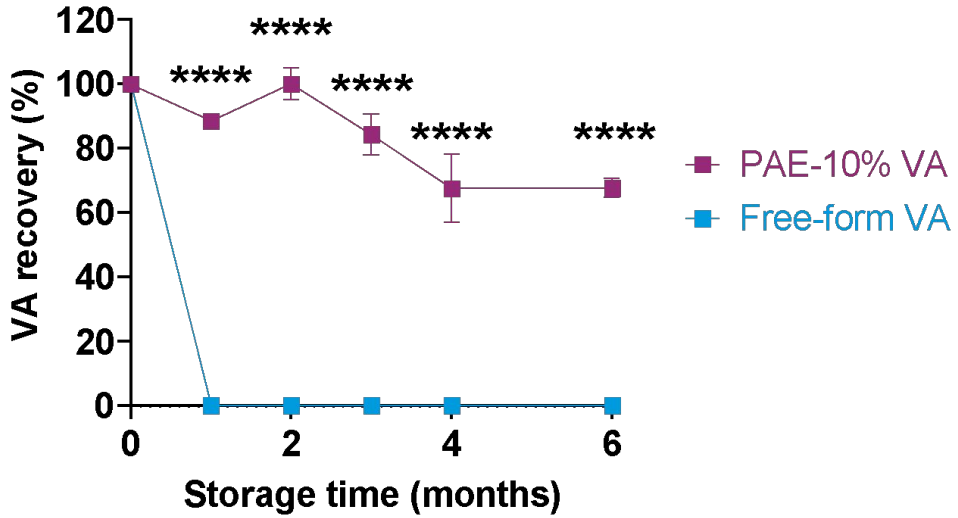
Cooking



After 2-hour boiling in water, **83%** of VA was protected by PAE MPs, compared to **6%** recovery of the free form

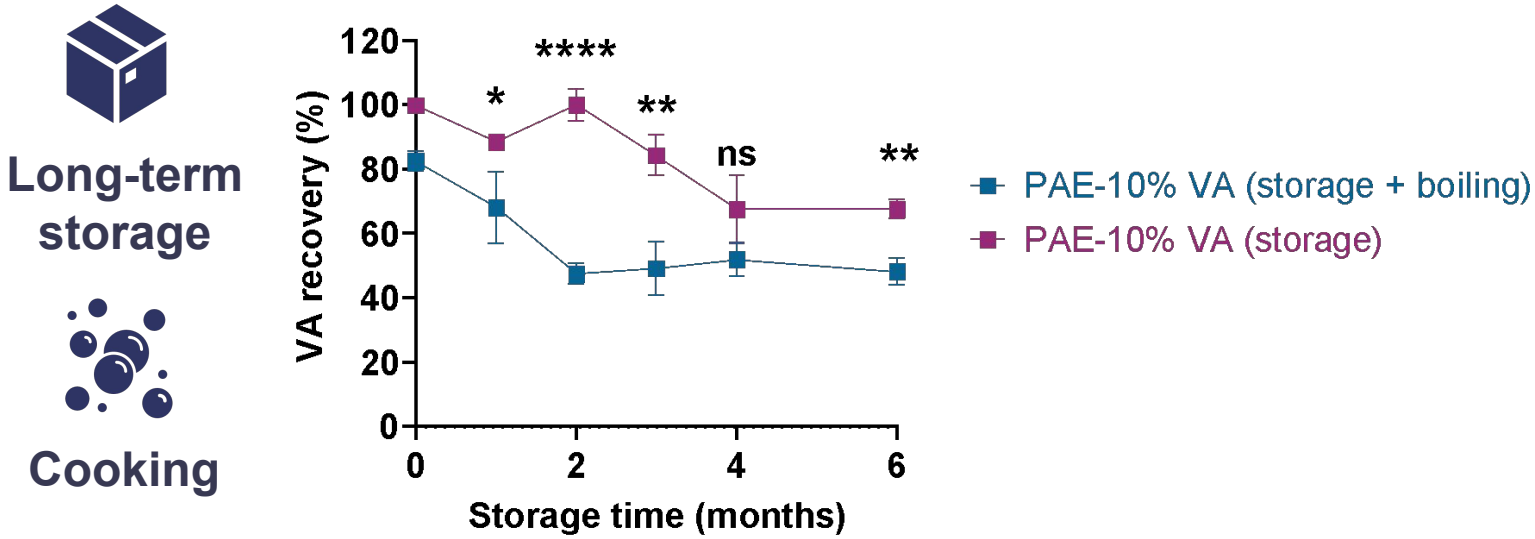
PAE MPs rendered effective protection for VA in long-term storage conditions

Long-term storage



After 6-month storage at 25 °C with 40% relative humidity, PAE MPs protected **68%** of VA, a significant improvement given that **no** free-form VA was recovered at the 1-month time point

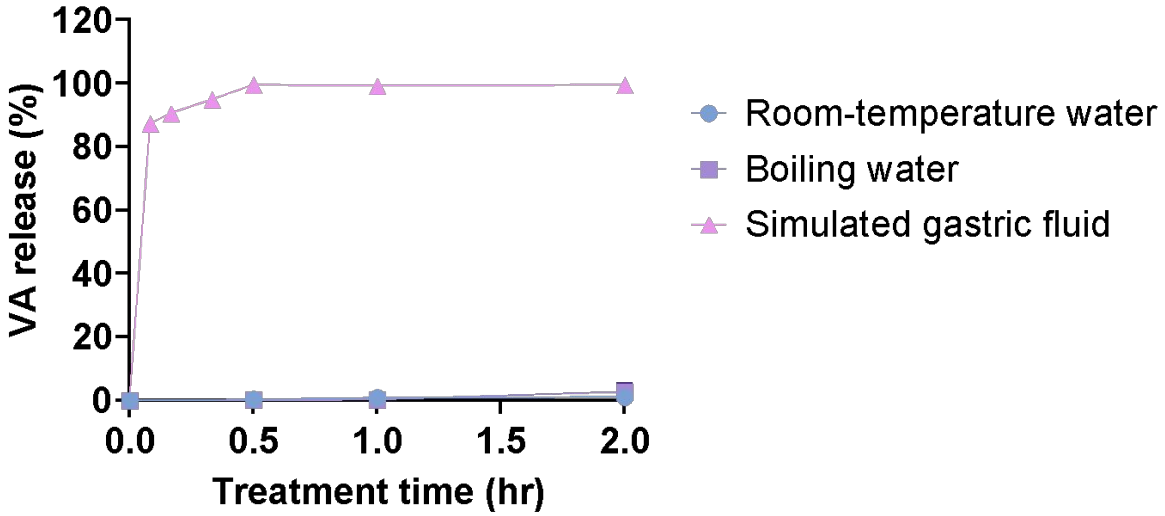
PAE MPs protected VA in cooking conditions after long-term storage



When the protection efficacy of VA was further challenged by 2-hour boiling in water after storage, **48%** of VA was recovered from PAE MPs at the 6-month time point

PAE MPs released VA efficiently in simulated gastric fluid

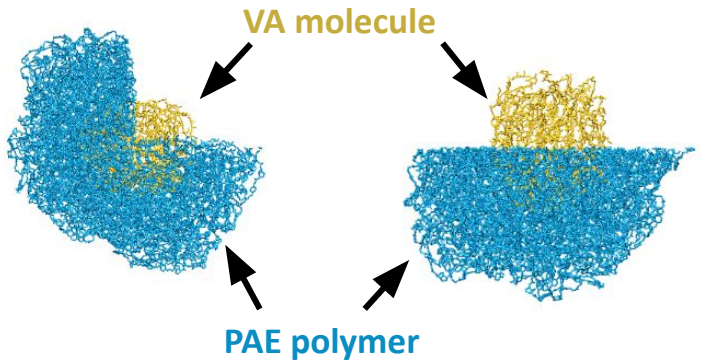
Release



After 10-min treatment of simulated gastric fluid under 37 °C, **90%** of VA was released from PAE MPs, while no release was observed in room-temperature or boiling water

Molecular dynamic simulation showed potent encapsulation of VA by PAE polymers

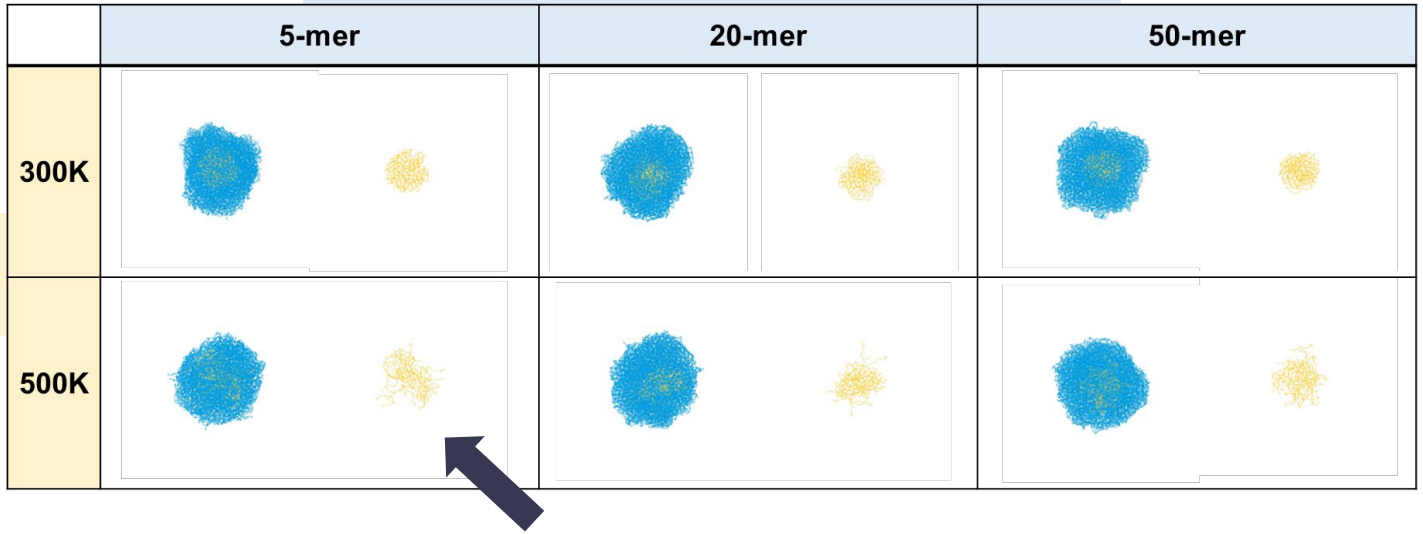
Computational method: Molecular dynamics (MD) simulation



Initial structure (simulation time = 0)

The effect of boiling water

The effect of polymer degradation



VA molecules diffuse away from the core but remained encapsulated even at high temperature (500K) with most degraded polymer (5-mer)

PAE MPs achieved thermal stabilization and controlled release for various micronutrients

Oil-soluble vitamin

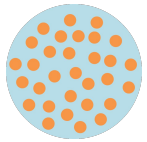
- VA (Retinyl palmitate)
- VD (Cholecalciferol)
- VE (Tocopherol)

Water-soluble vitamin

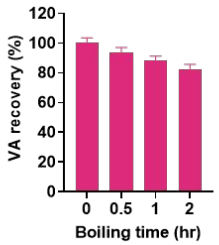
- VC (Ascorbyl palmitate)

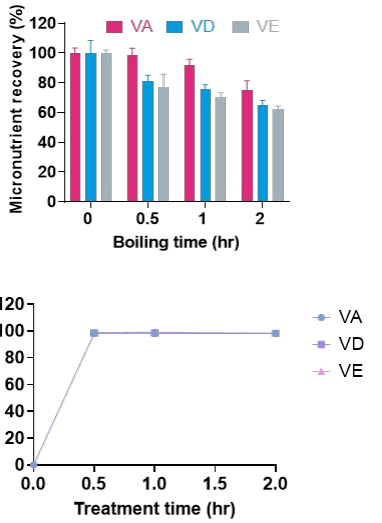
Water-soluble mineral

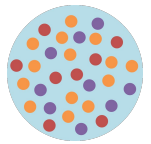
- Iron (Ferrous sulfate)
- Zinc (Zinc sulfate)



Individual Encapsulation







Collective Encapsulation

PAE MPs achieved thermal stabilization and controlled release for various micronutrients

Oil-soluble vitamin

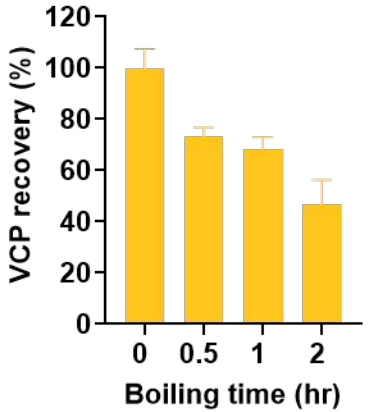
- VA (Retinyl palmitate)
- VD (Cholecalciferol)
- VE (Tocopherol)

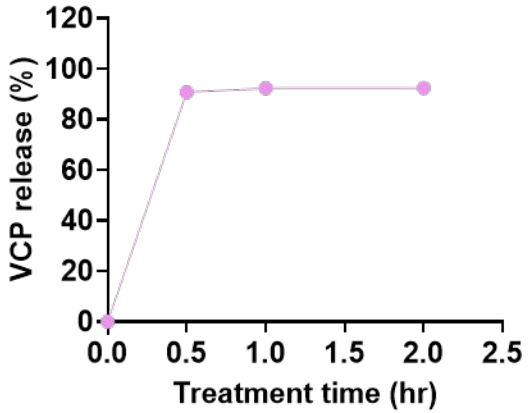
Water-soluble vitamin

- VC (Ascorbyl palmitate)

Water-soluble mineral

- Iron (Ferrous sulfate)
- Zinc (Zinc sulfate)





PAE MPs achieved thermal stabilization and controlled release for various micronutrients

Oil-soluble vitamin

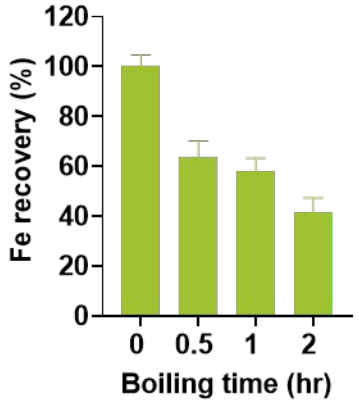
- VA (Retinyl palmitate)
- VD (Cholecalciferol)
- VE (Tocopherol)

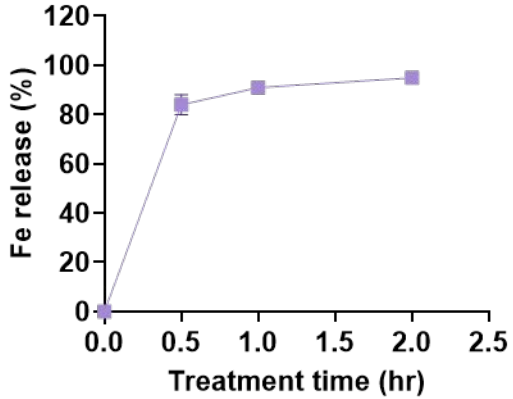
Water-soluble vitamin

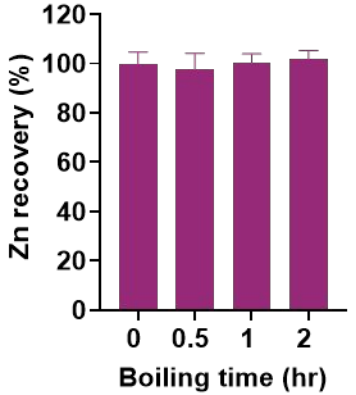
- VC (Ascorbyl palmitate)

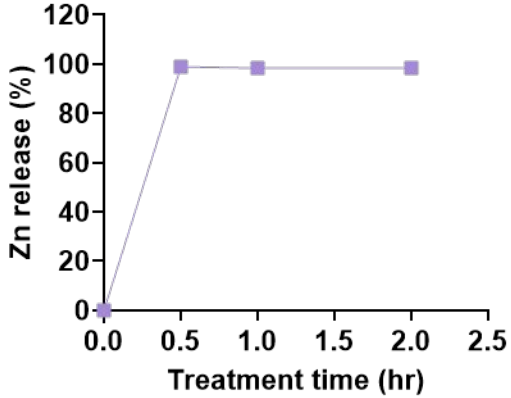
Water-soluble mineral

- Iron (Ferrous sulfate)
- Zinc (Zinc sulfate)





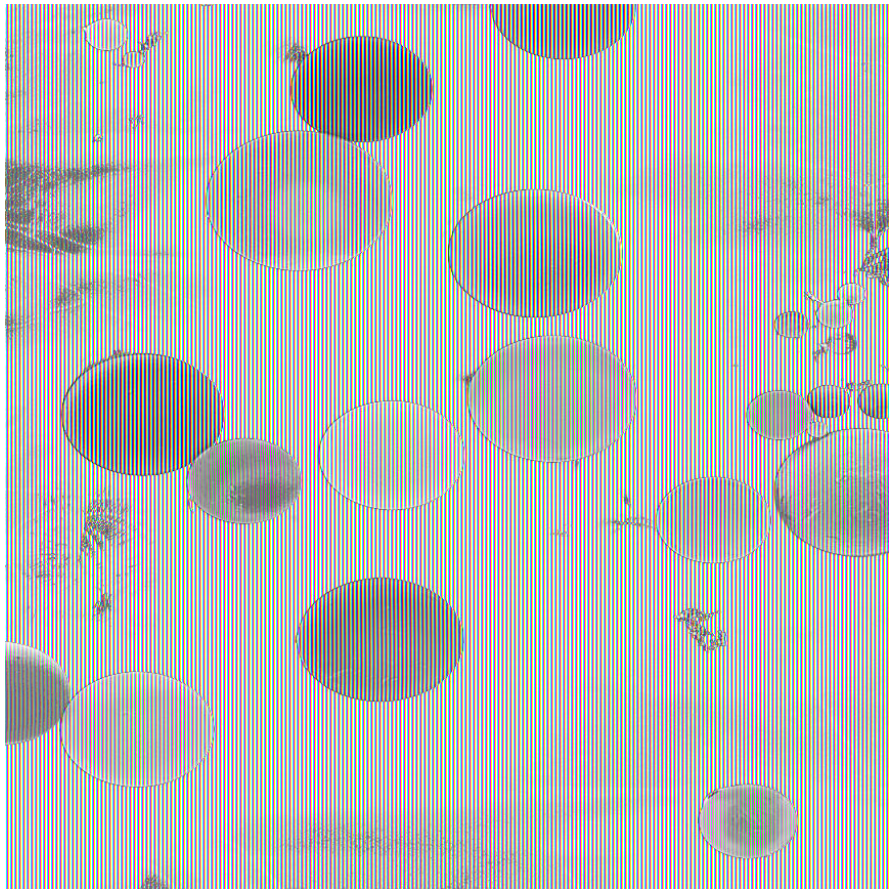




Summary

PAE-based MP platform for micronutrient stabilization and oral delivery

- Developed a group of PAE polymers and landed one composition as the best candidate
- Effectively stabilized VA in cooking and long-term storage conditions
- Efficiently released VA in simulated gastric fluid for oral delivery
- Achieved encapsulation, stabilization, and controlled release of multiple micronutrients



2022 Koch Institute Image Award

Acknowledgement

PhD advisors:

Dr. Ana Jaklenec

Dr. Robert Langer

Micronutrient team:

Ruiqing Xiao

Tianyi Jin

Xinyan Pan

Ruizhe He

Shahad Alsaiari

Aranda Duan

Alicia Lau