# *From Molecule to Patient: A Biotech Perspective*

Dr. Robert Langer

The New York Times

PERSONAL HEALTH

# *The Cost of Not Taking Your Medicine*

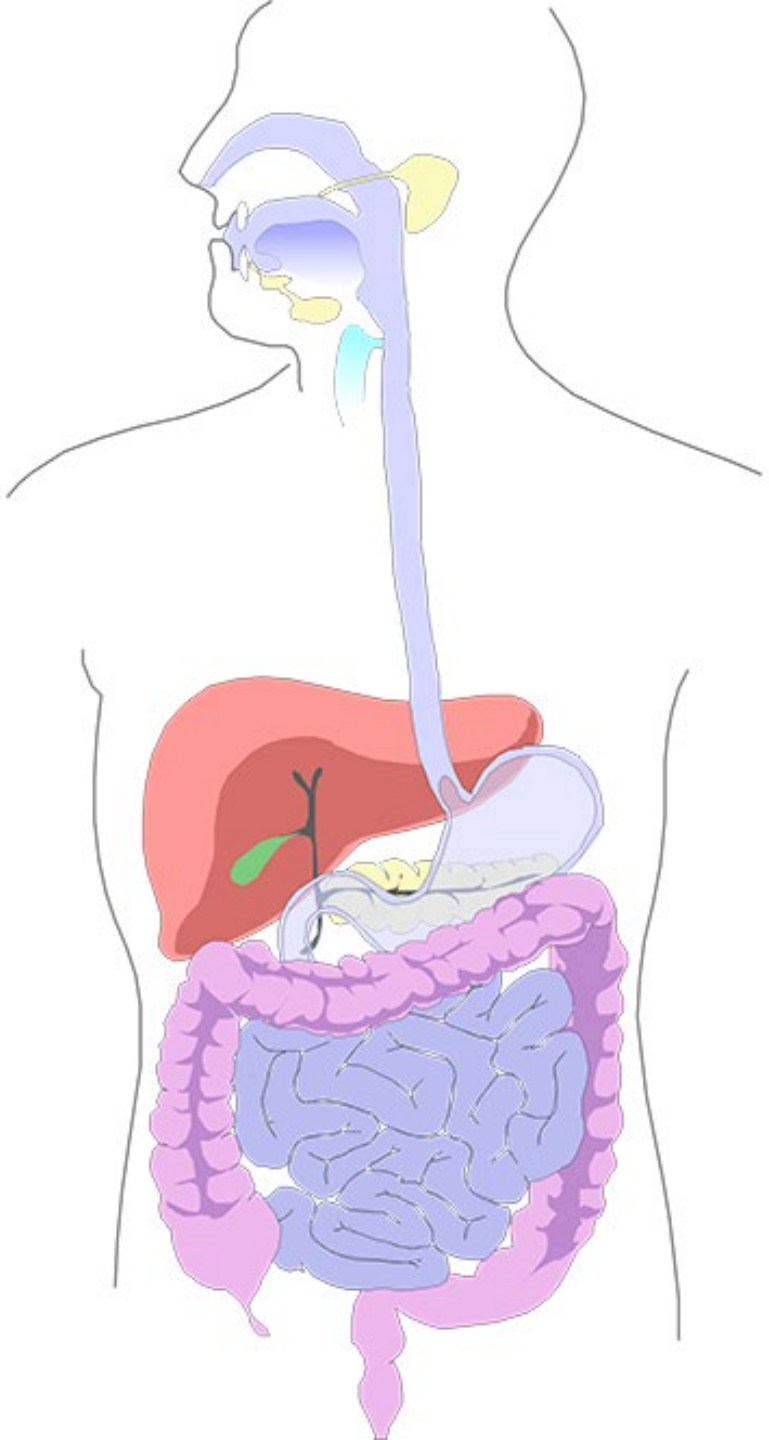
By Jane E. Brody

April 17, 2017

Credit: Paul Rogers

This lack of adherence, the Annals authors wrote, is estimated to cause approximately 125,000 deaths and at least 10 percent of hospitalizations, and to cost the American health care system between $100 billion and $289 billion a year.

Studies have shown that a third of kidney transplant patients don't take their anti-rejection medications, 41 percent of heart attack patients don't take their blood pressure medications, and half of children with asthma either don't use their inhalers at all or use them inconsistently.



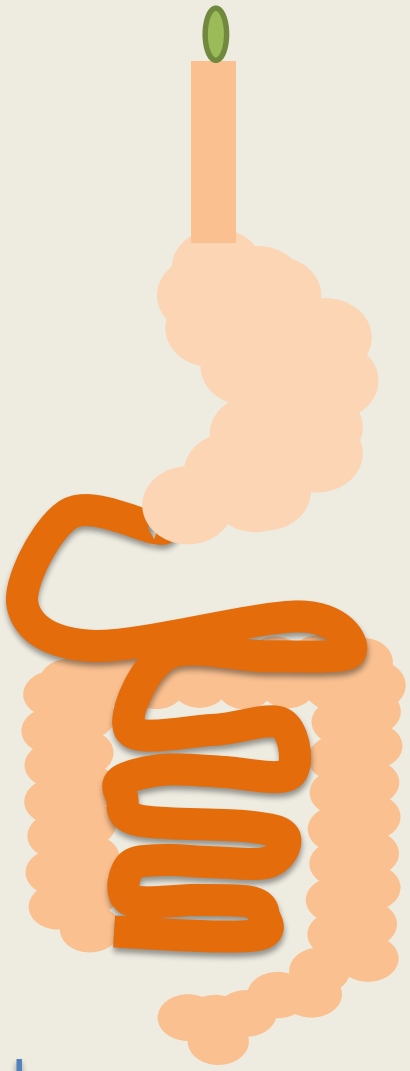
# Challenges with oral drug delivery

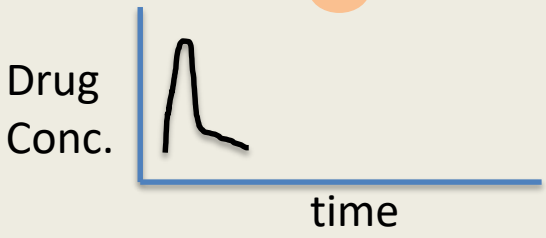
Oral Delivery and GI residence of a specific drug formulation is limited by GI transit time

Whole Gut Transit Time: ~1 day

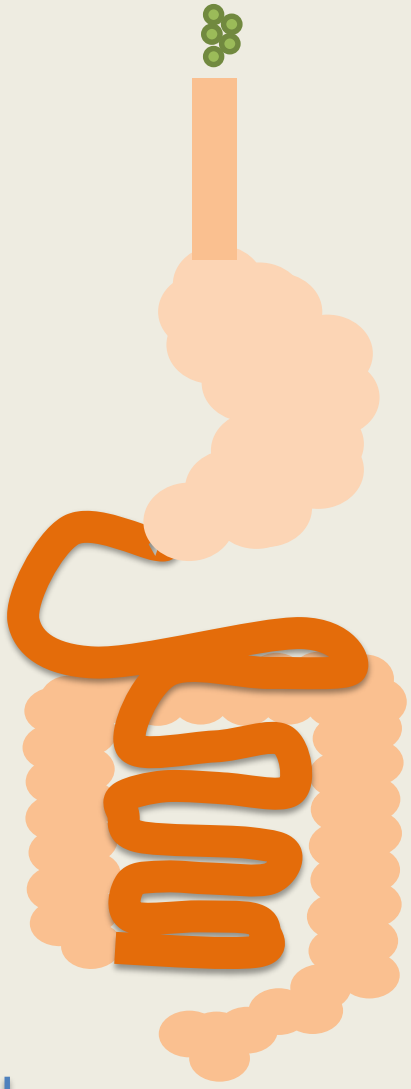
Chaddock et al. *Neurogastr. Motil,* 2014

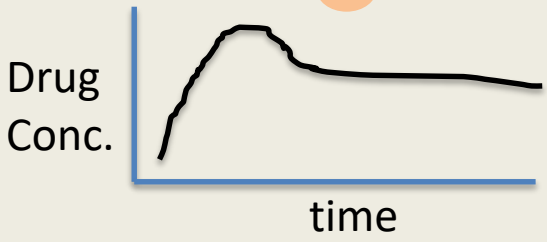
Standard Capsule



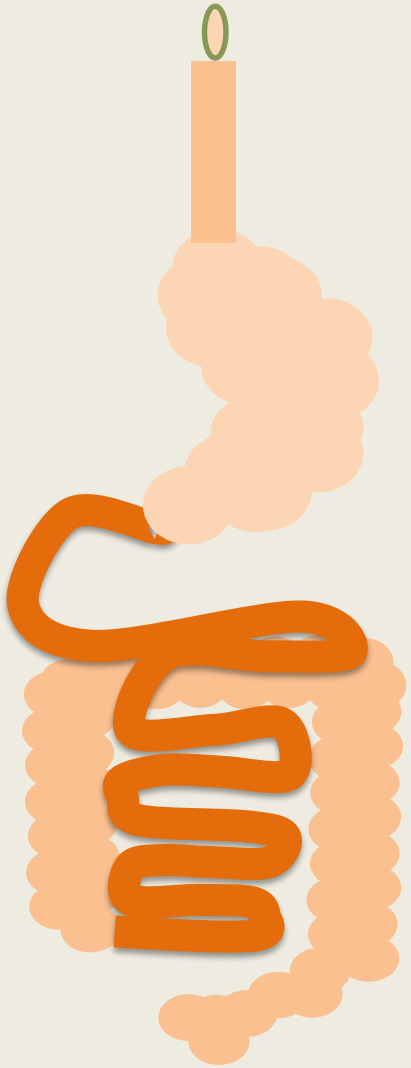



GI Transit Slowed






GI Retention



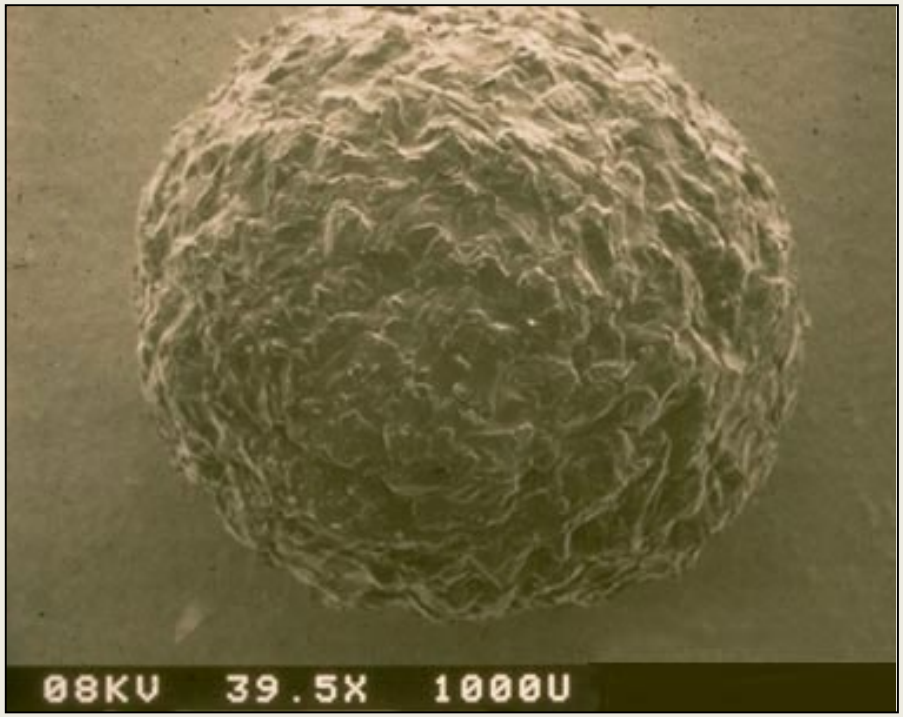
- Can we control drug release rates?
- Can we deliver drug for a long time?
- Can we control polymer degradation?
- Can we control polymer shape?
- Can we do all this safely and relatively inexpensively?

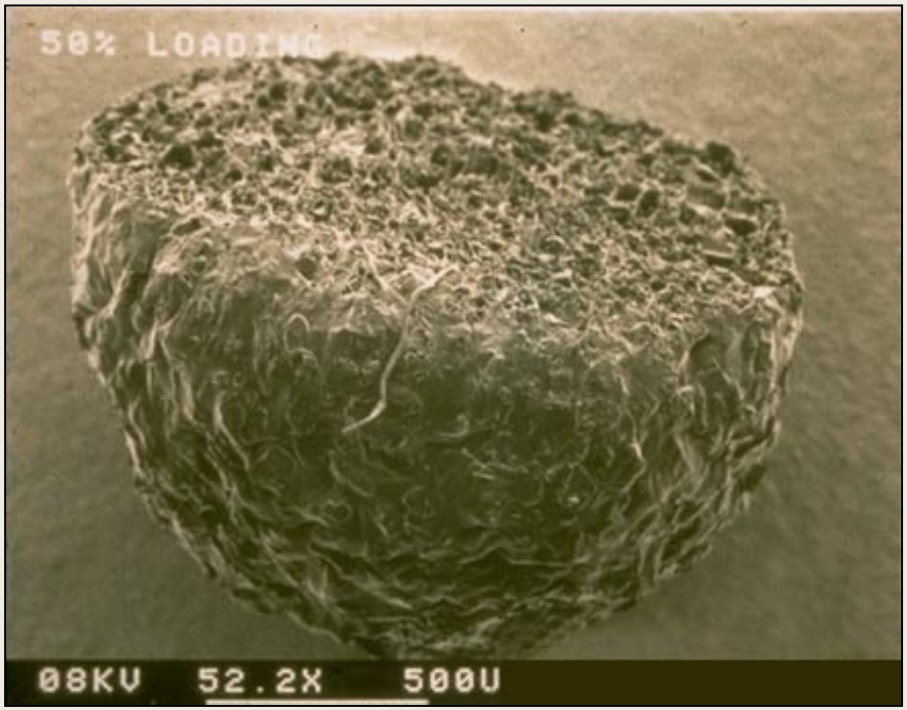
# This approach will not work because

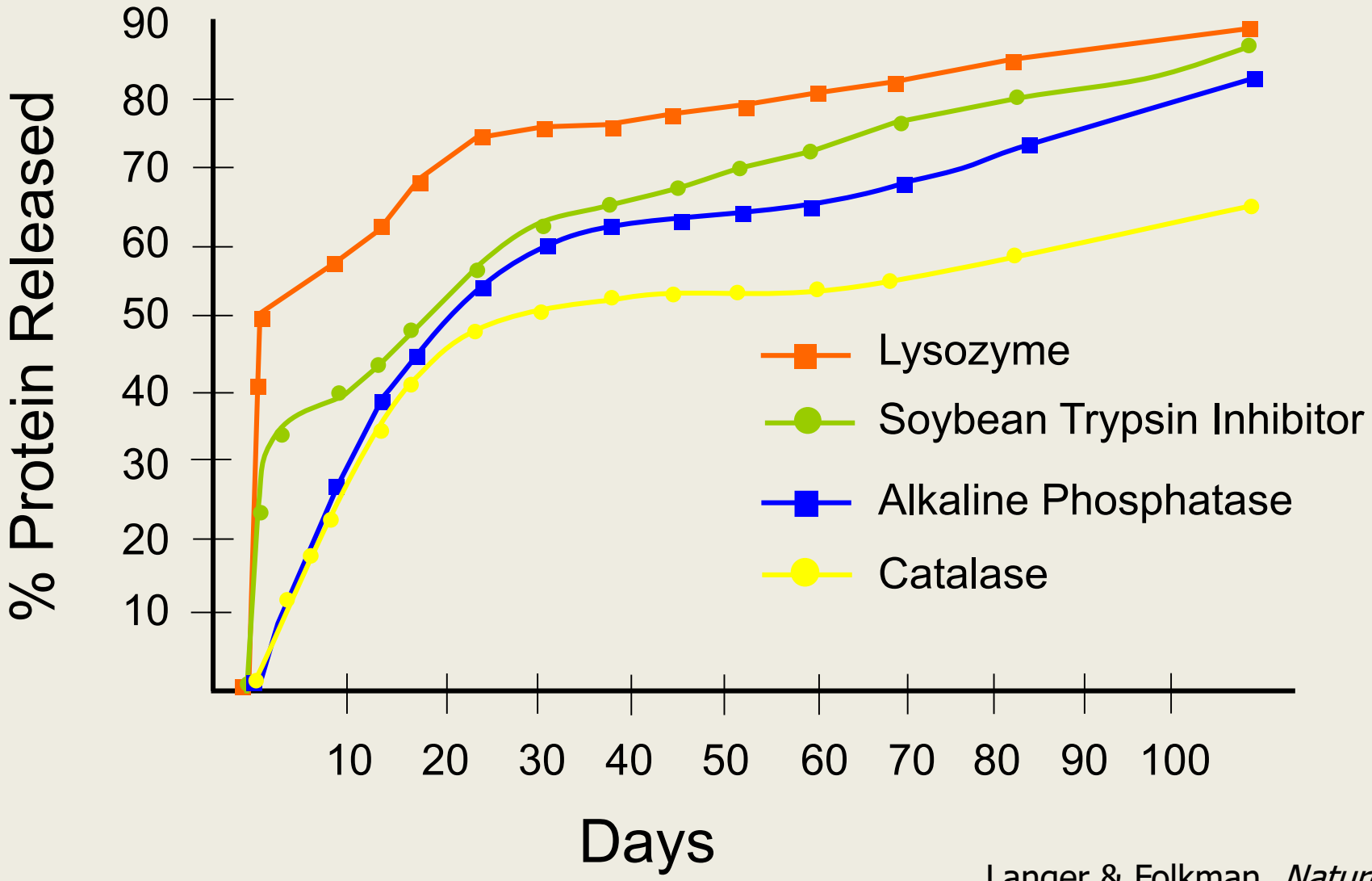
- Large molecules cannot slowly diffuse through solid polymers

"The use of polymer matrices for slow release systems has been virtually restricted to small molecules."

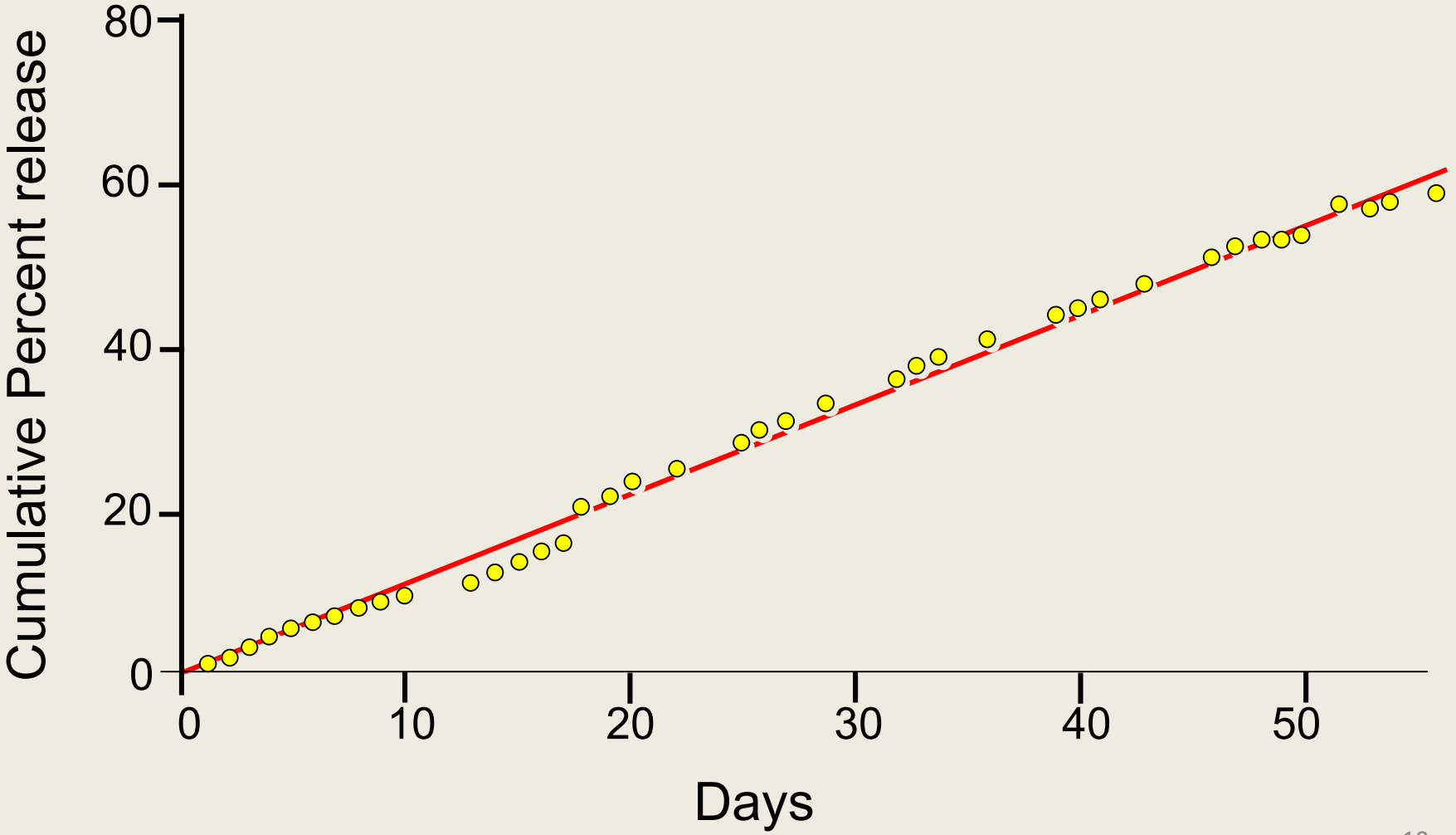
*Chemical and Engineering News*, 1977


08KV 39.5X 1000U


50% LOADING
08KV 52.2X 500U




Langer & Folkman, *Nature*, 1976

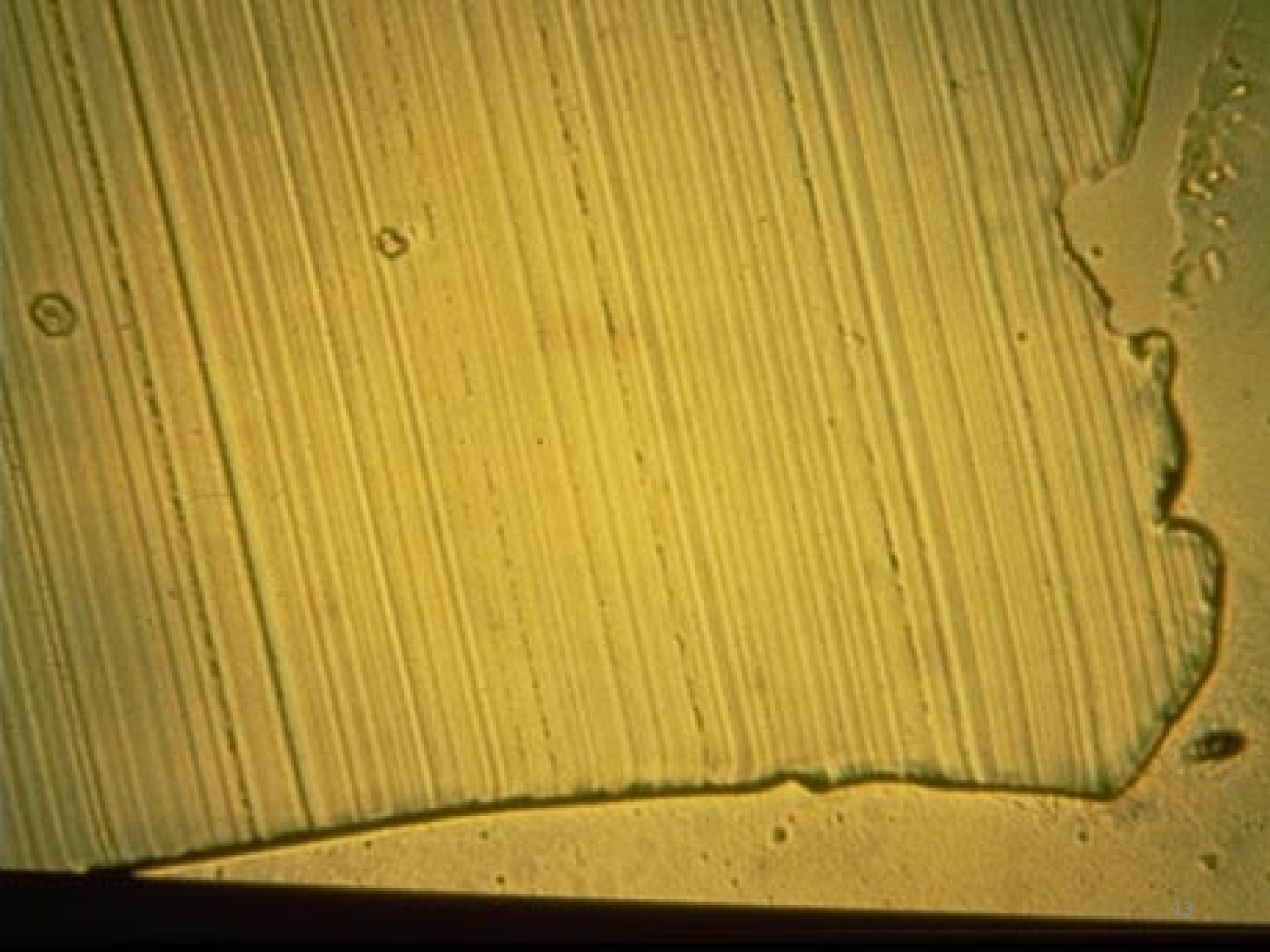

Cumulative Percent release
80
60
40
20
0
0
10
20
30
40
50
Days

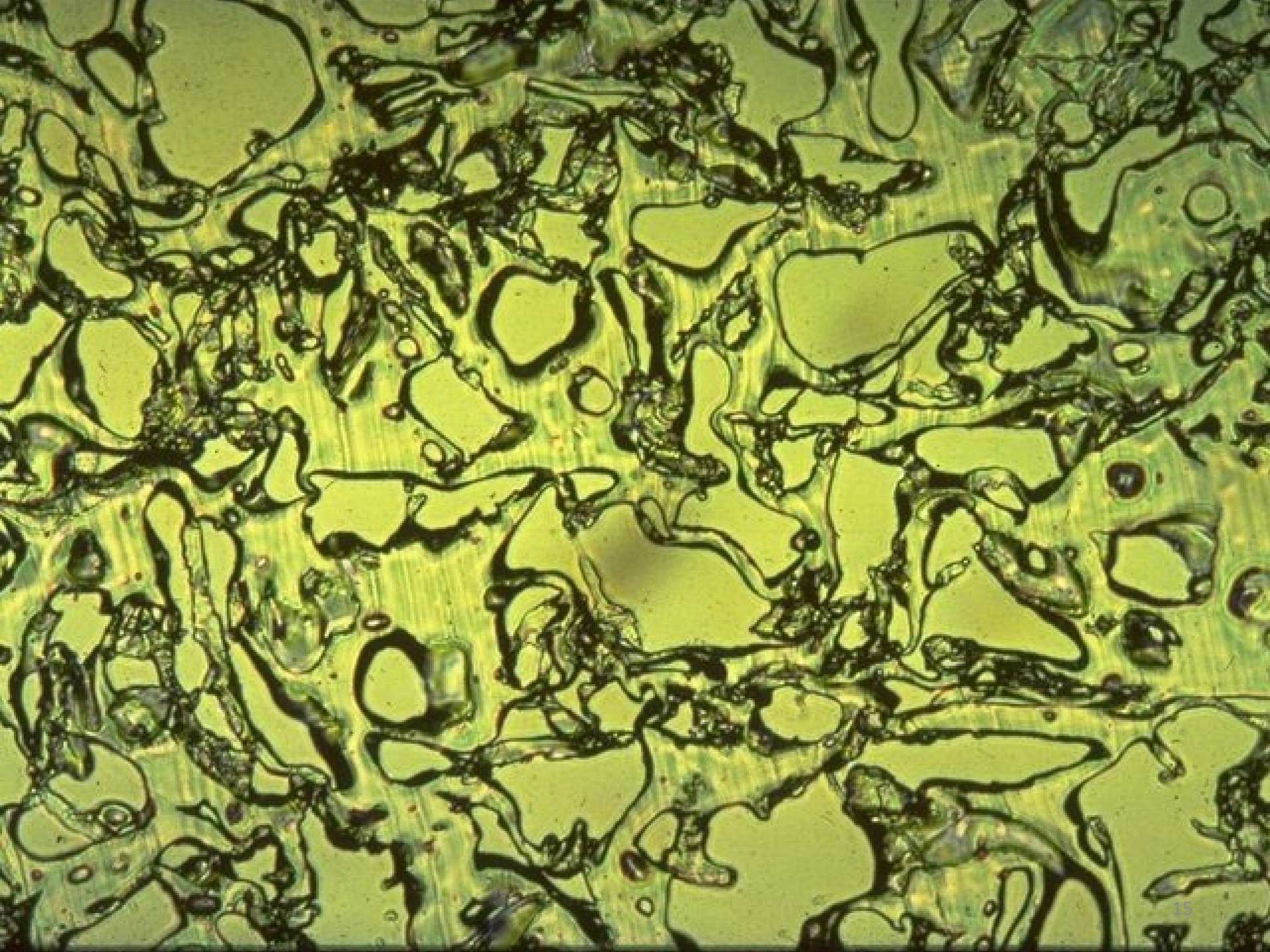
# This approach will not work because

- Large molecules cannot slowly diffuse through solid polymers
- Organic solvents will denature peptides or proteins

“One evening, I went to a faculty dinner at a Chinese restaurant with Bob Langer and some senior MIT professors. A senior scientist sat quizzing us while smoking a cigar. When the older scientist heard Langer’s concepts for polymeric drug delivery, he blew a cloud of smoke in Langer’s face and said, “You better start looking for another job.” I thought I was in a Fellini movie.”

Professor Michael Marletta





"Generally the agent to be released is a relatively small molecule with a molecular weight no larger than a few hundred. One would not expect that macromolecules, e.g. proteins, could be released by such a technique because of their extremely small permeation rates through polymers. However, Folkman and Langer have reported some surprising results that clearly demonstrate the opposite."

-Stannett, Koros, Paul, Baker, Lonsdale, *Adv. Poly. Sci*., 1979.

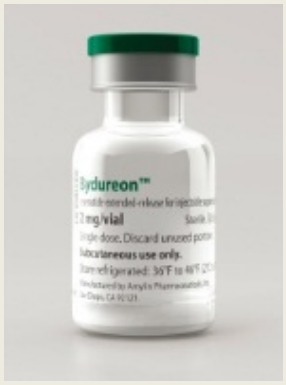
# U.S. Patent 4,391,797: Folkman and Langer

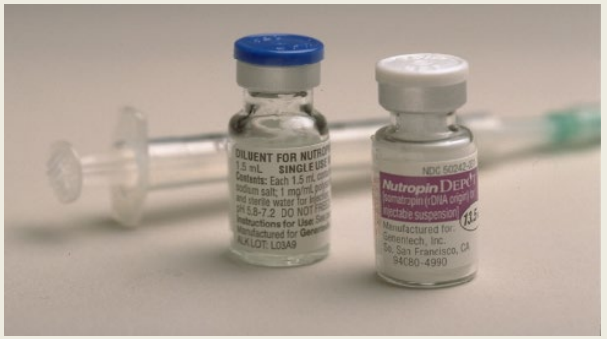
- Two phase system
- 1st phase – polymer with water sorbtivity not greater than 50%
- 2nd phase – agglomerated macro- molecular material of MW at least 1000


Decapeptyl LP
3 mois


Vivitrol


EXPAREL
1.3%
266 mg / 20 mL (13.3 mg/mL)

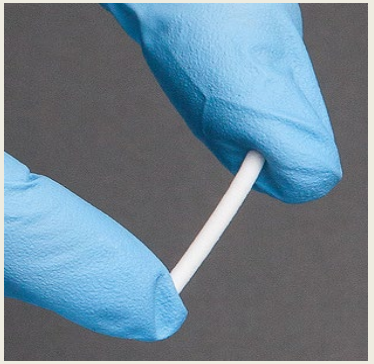

Sydureon


Nutropin DEPOT

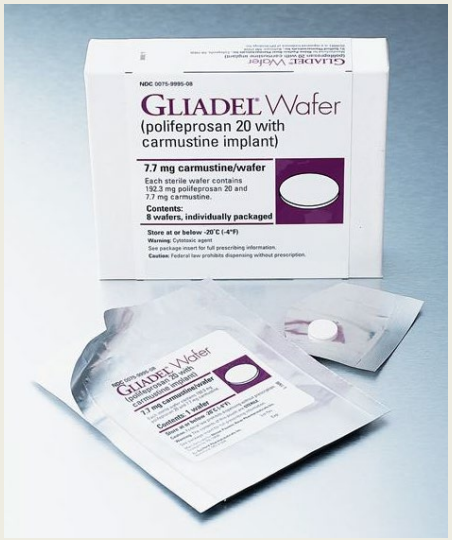

SURGIFLO

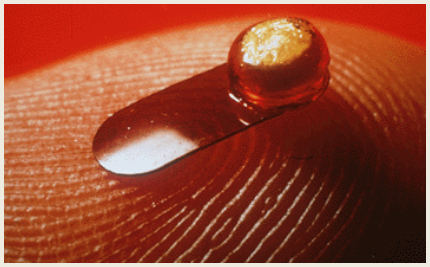

Floseal


LUPRON DEPOT

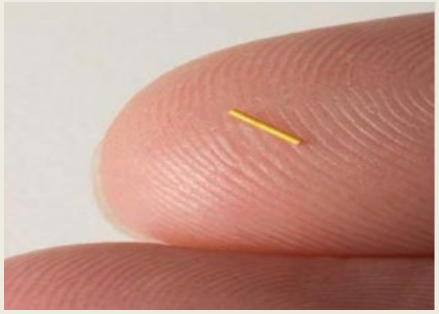


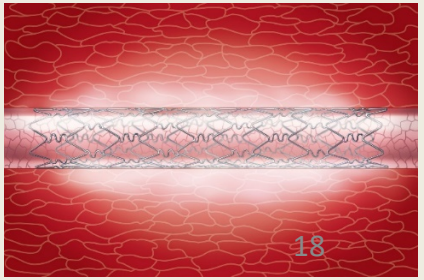

Zoladex 3-month
10.8 mg goserelin


GLIADEL Wafer
(polifeprosan 20 with carmustine implant)
7.7 mg carmustine/wafer

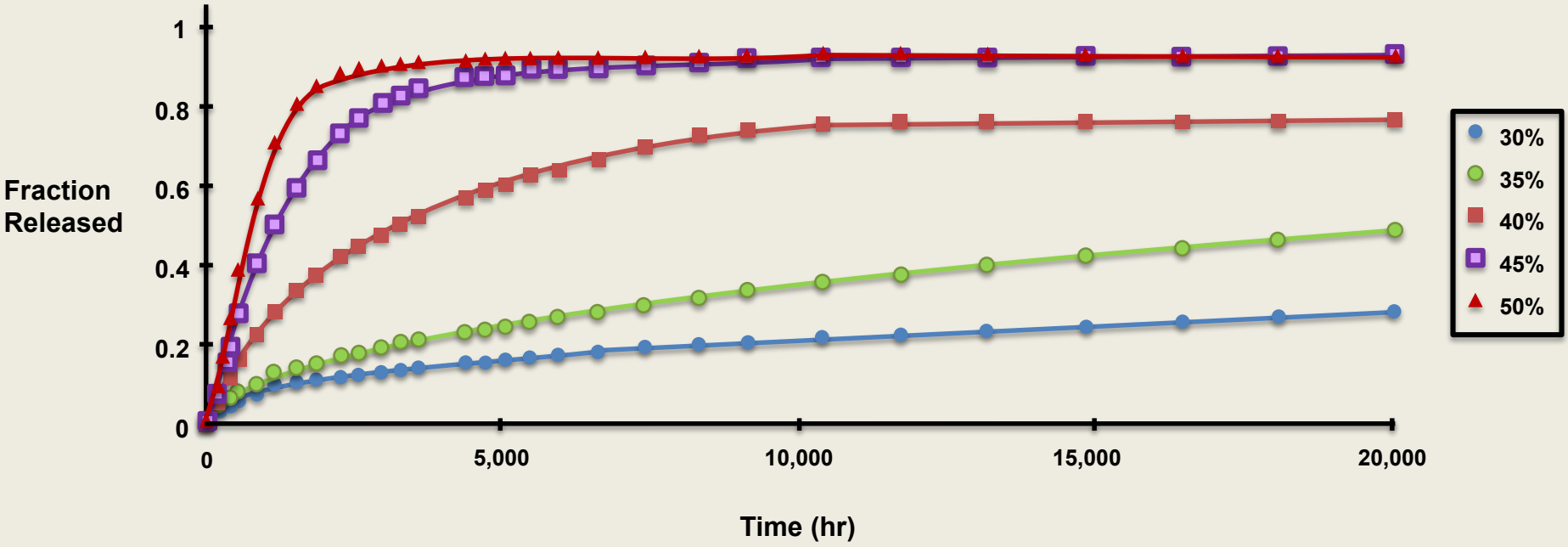



50 mg
37.5 mg
25 mg
RisperdalCONSTA



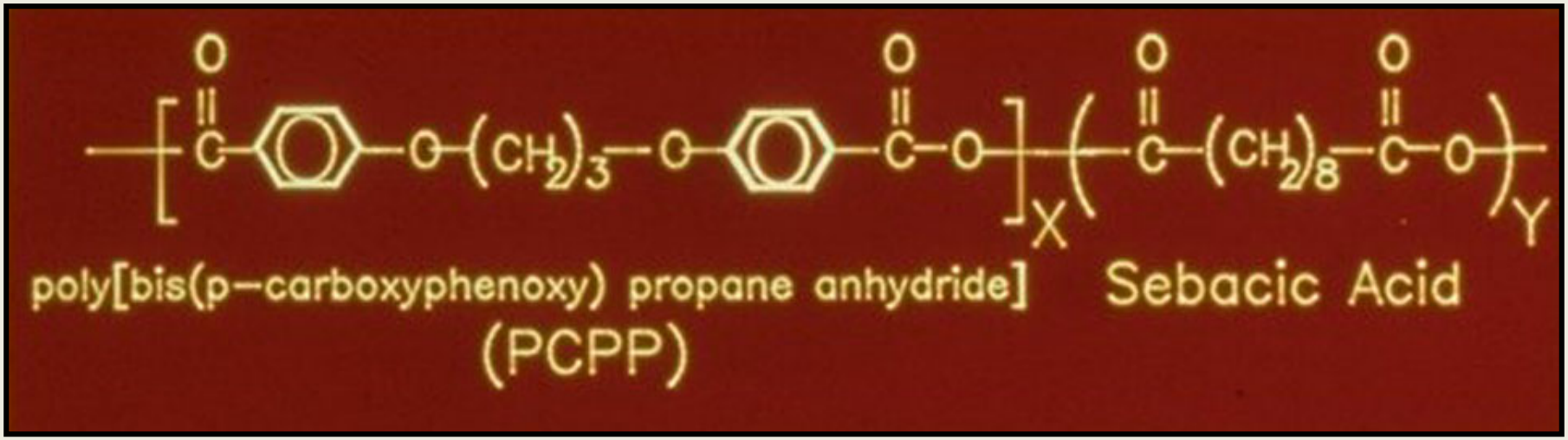


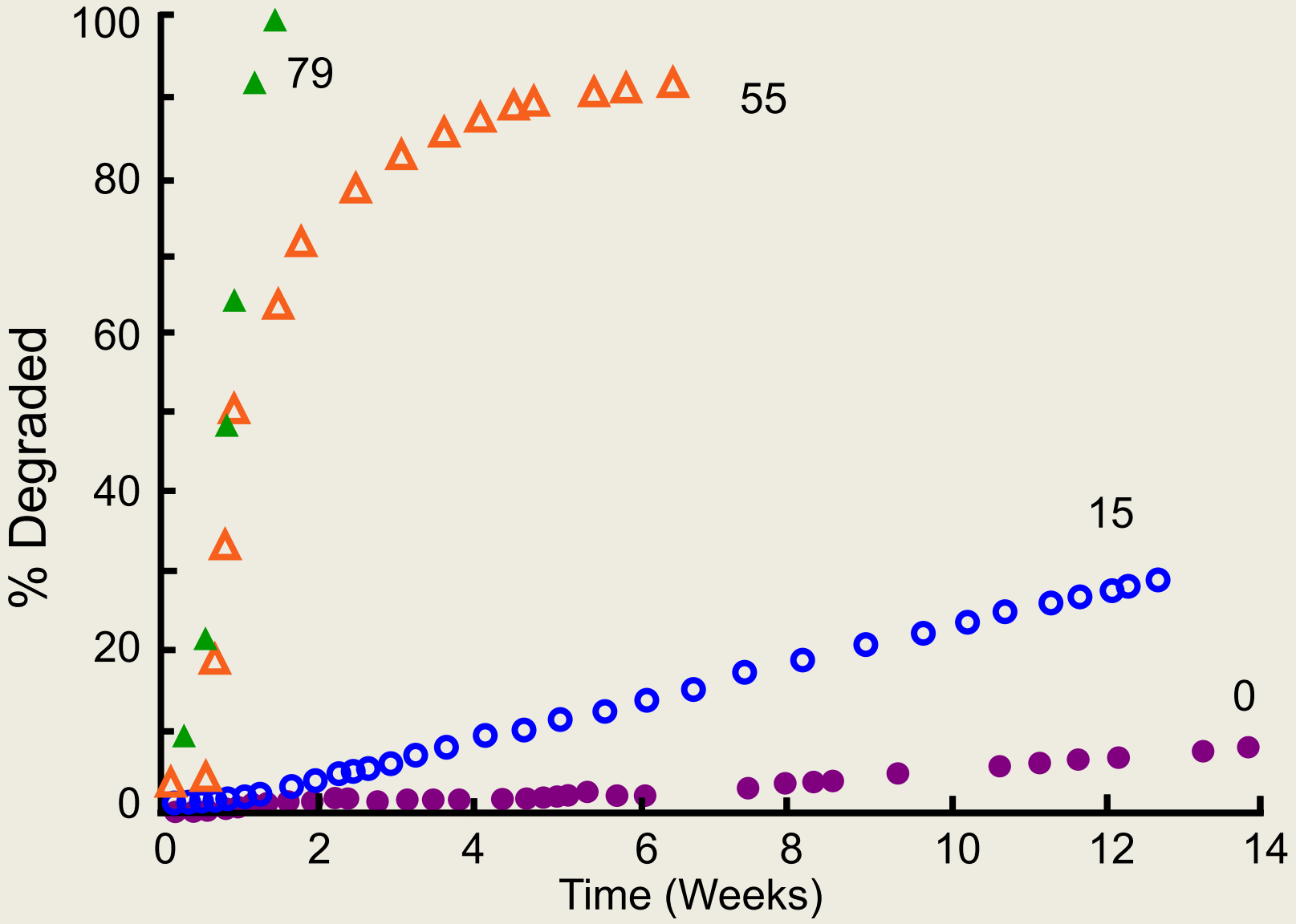
# Can we deliver drugs for a long time?


Fraction Released
1
0.8
0.6
0.4
0.2
0
0
5,000
10,000
15,000
20,000
Time (hr)
30%
35%
40%
45%
50%

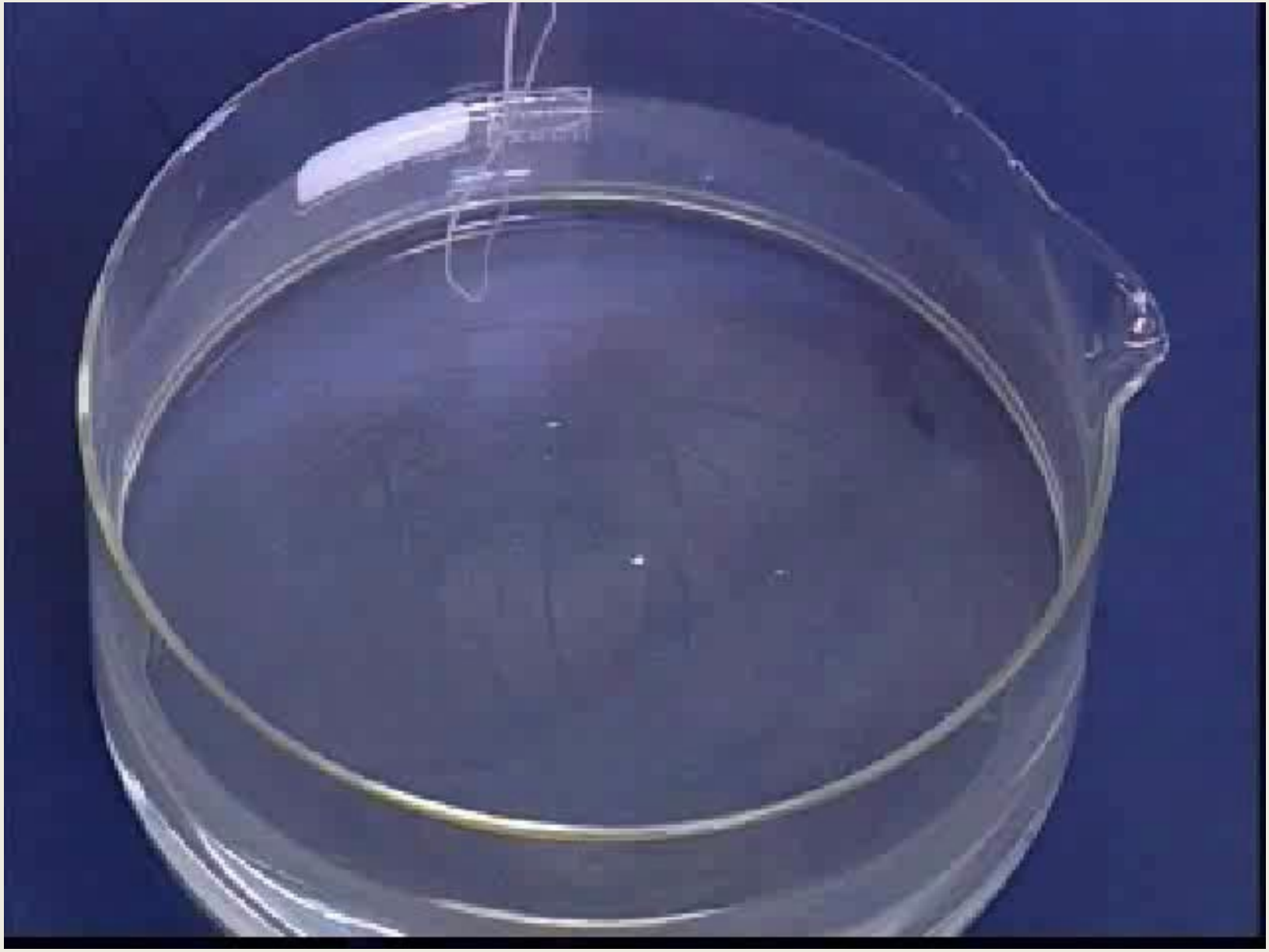
# Can we control polymer degradation?

# Structure of the polymer



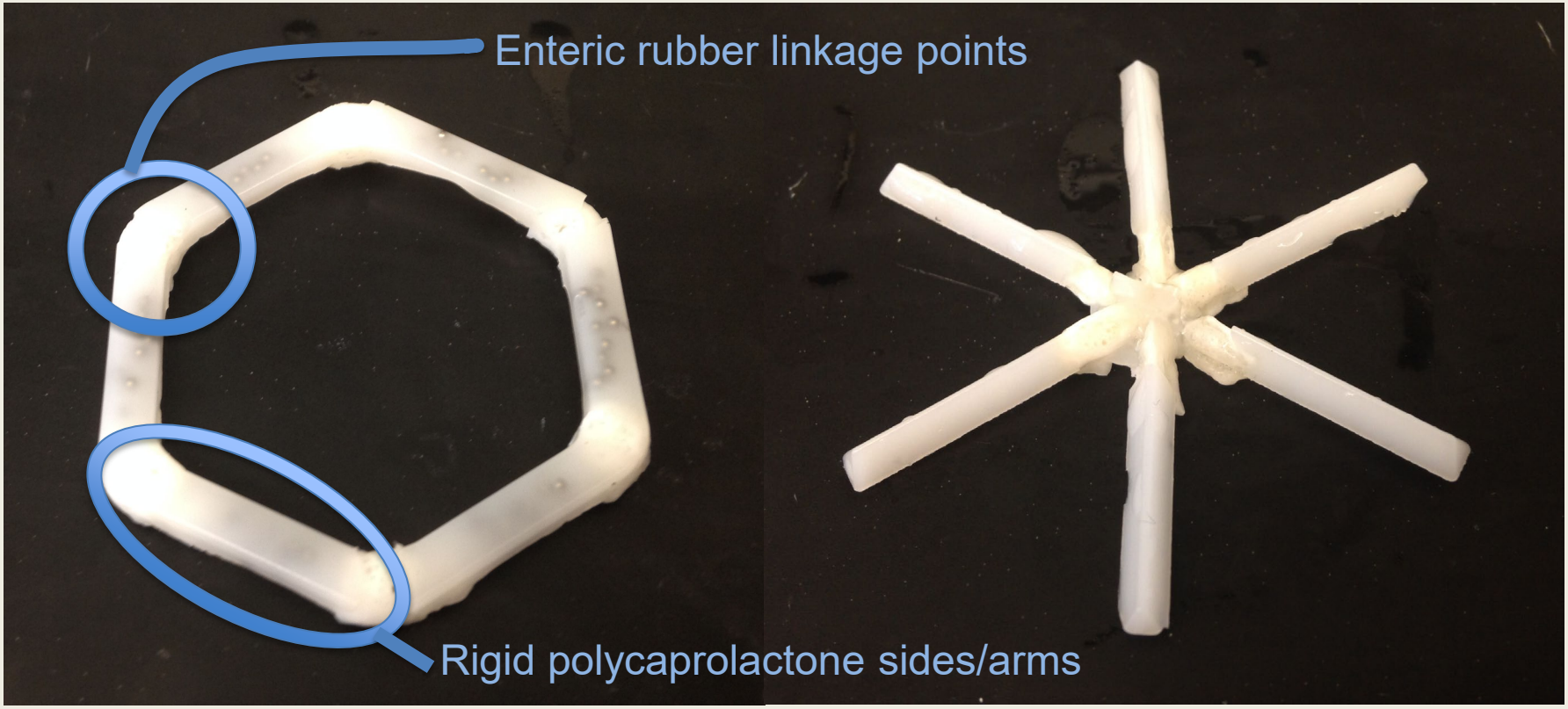

100
80
60
40
20
0
% Degraded
79
55
15
0
0
2
4
6
8
10
12
14
Time (Weeks)

# Can we control polymer shape?



# Can we do all this safely and effectively?

# Initial prototypes



# Current formulations are comparable in size to some OTC products

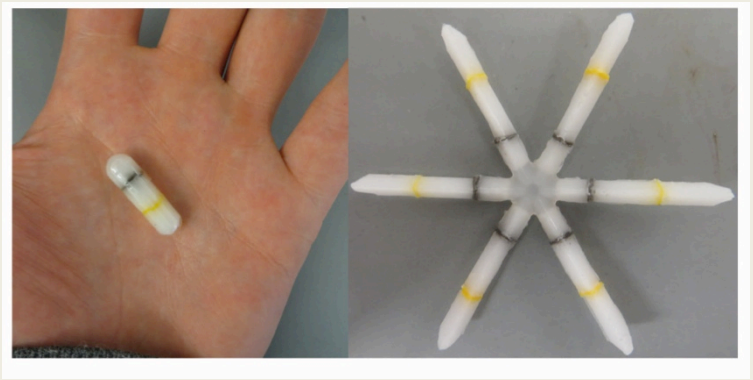
Probiotics

Multivitamins


Fish Oil

Current versions use 00 capsules

Dosage Form



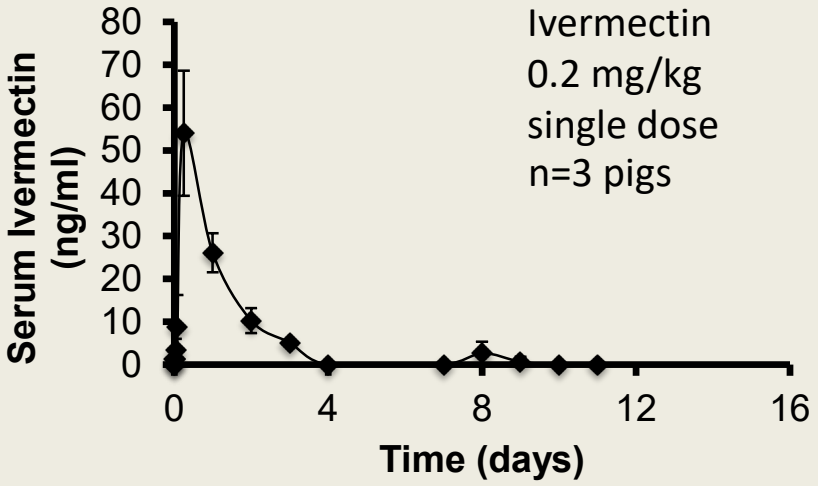
# Ivermectin: A safe, versatile antihelminth with wide applicability including vector control of malaria

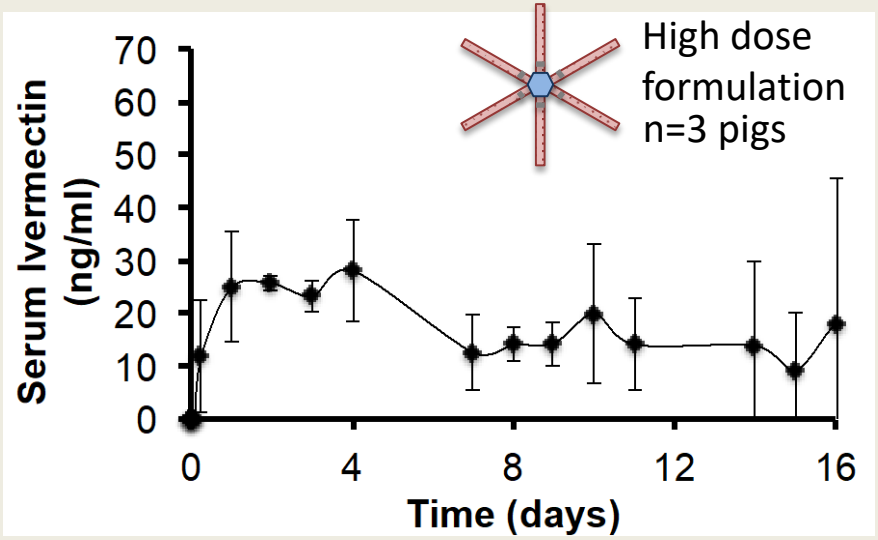
Modeling results from our collaborators support the development of extended release ivermectin

- Edward Wenger and Philip Eckhoff at the Institute for Disease Modeling/Global Good
- Hannah Slater and Azra Ghani at Imperial College
- Maintain Invermectin at 6ng/ml for over 2 weeks

# Sustained oral ivermectin

**Goal**: a single encounter oral therapy that could be widely administered in Africa for sustained delivery of an anti-malarial / anti-helminth



# Safety

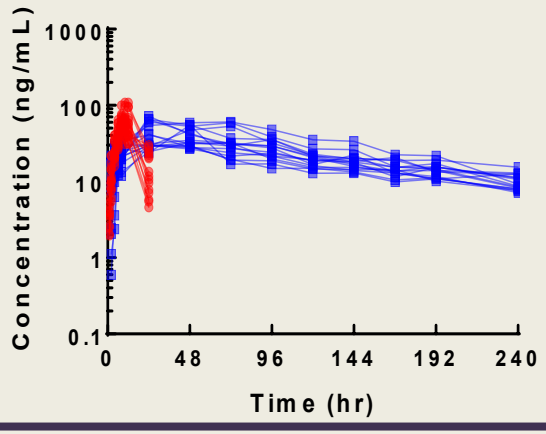
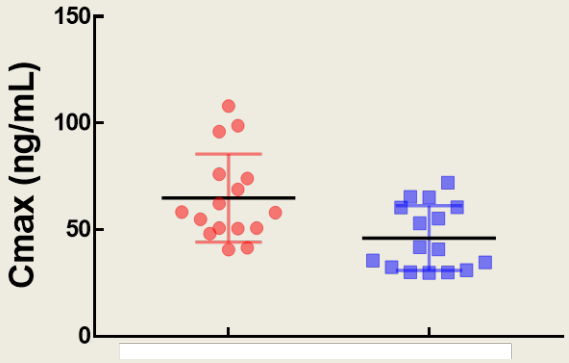
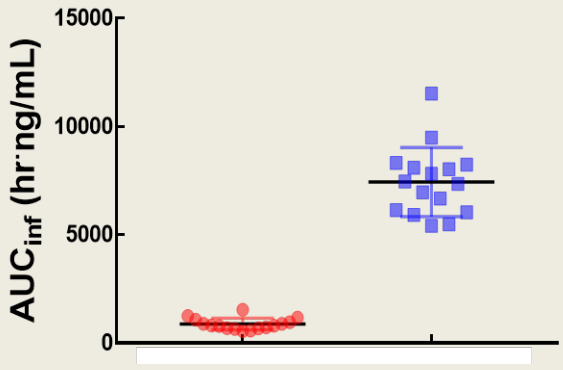
We have tested versions of this delivery platform in over 300 pig Experiments

- No adverse events
- No clinically apparent symptoms, no obstruction, no perforation, no change in appetite, weight gain, or stool frequency
- No mucosal injury or gastric ulceration visible on endoscopic evaluation or autopsy

# Preclinical Pharmacokinetics Proof of Concept

Comparison of a Commercial Single Daily Dose Extended Release Product to Lyndra 7-Day Product of Single Agent:

- Achieved 7 fold higher AUC with a lower Cmax
- Potentially lower inter-subject variability

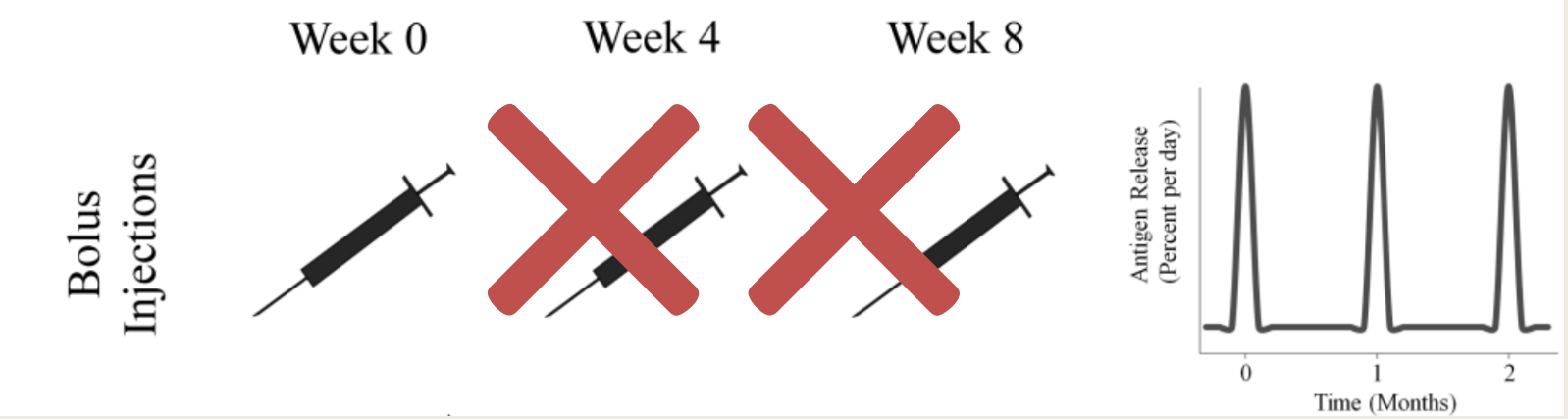
| Therapeutic Effect Over 7 Day Period | Lower Peak Cmax<br>No Burst Release of Drug | Matched Overall Exposure<br>7-Day AUC is 7 times higher |
|---|---|---|
|  |  |  |



Unpublished data, Large Animal (Beagles) Preclinical Studies

# Single-Injection Vaccination

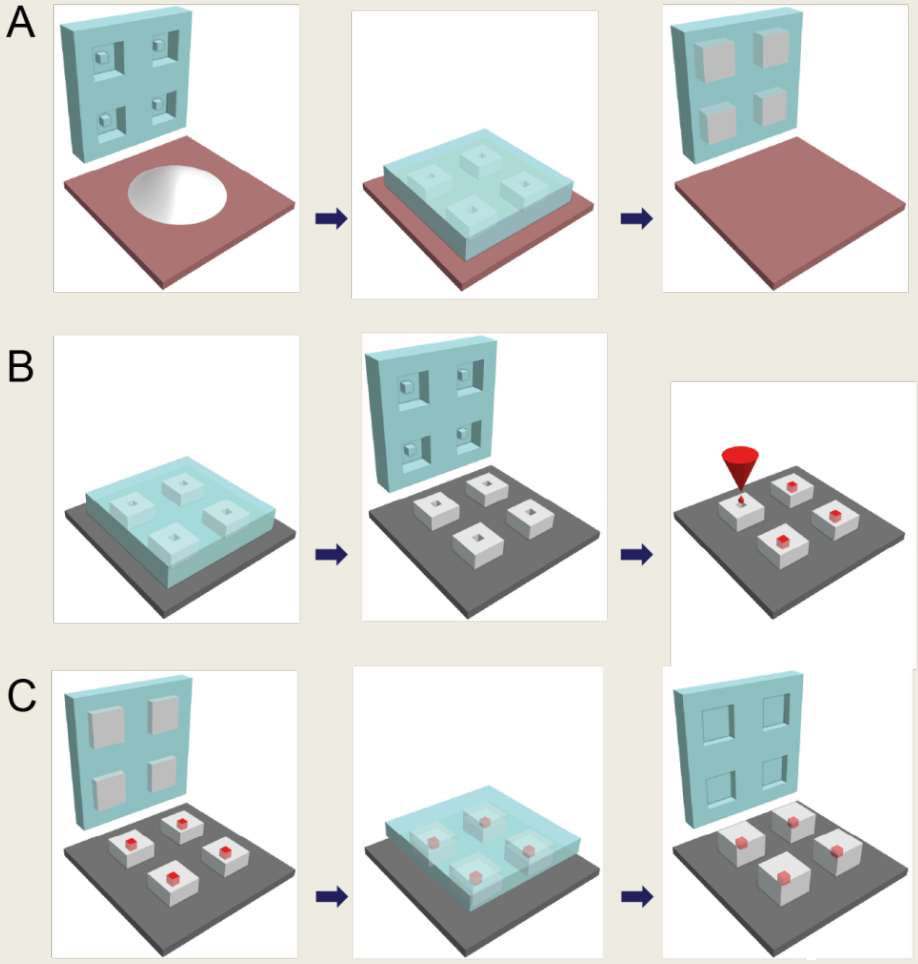
- 25 million infants remain under-immunized each year[1] contributing to 1.5 million deaths[2]
- 10 million of these infants receive at least one dose of a vaccine, but remain at risk[1]
- Single-injection vaccination could treat this patient population without any other change in infrastructure[3]



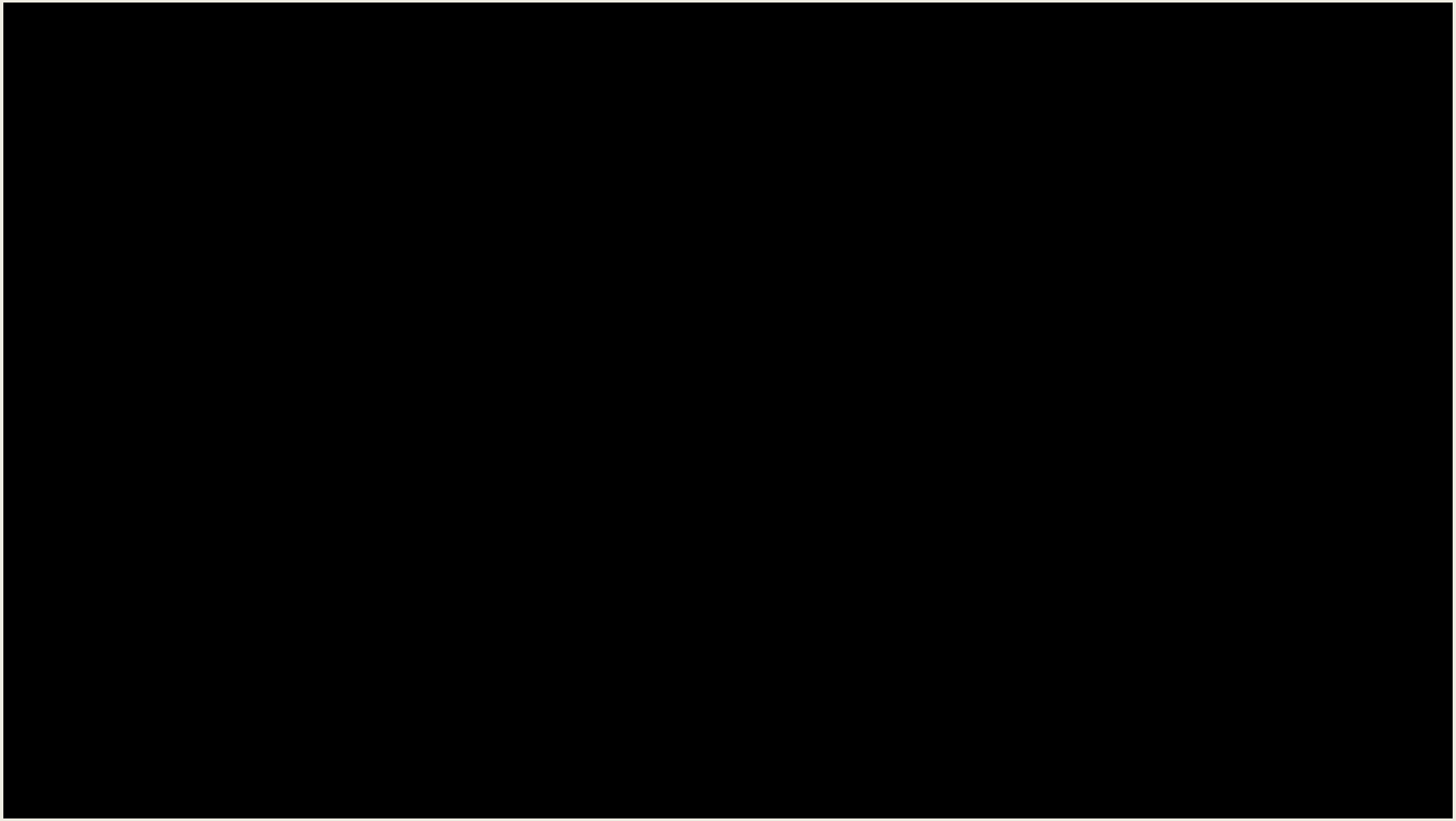

[1]World Health Organization, MMWR Weekly, 2015.
[2]World Health Organization, Immunization Coverage Fact Sheet, July 2017.
[3]McHugh KJ, J Control Release, 2016.

# Micromolded Particle Fabrication

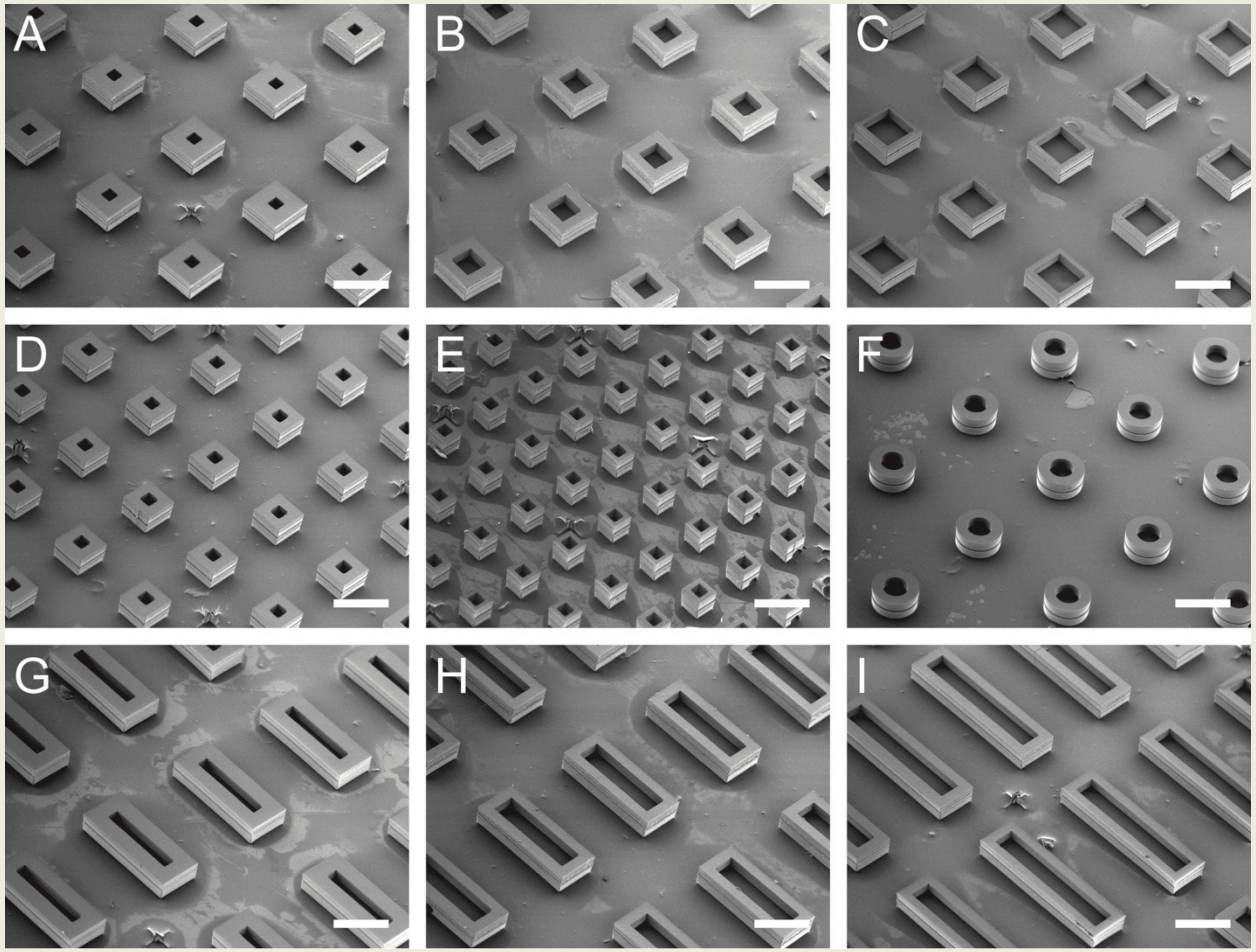
1. Particle molding via soft lithography
2. Inkjet filling using a BioDot picoliter dispensing system
3. Particles aligned and sealed using heat-assisted microtransfer molding



# Microparticle Fabrication

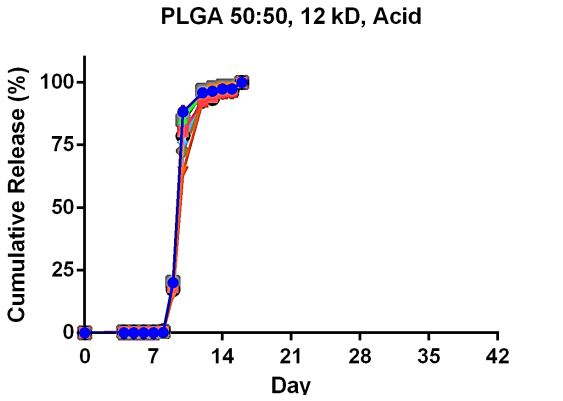


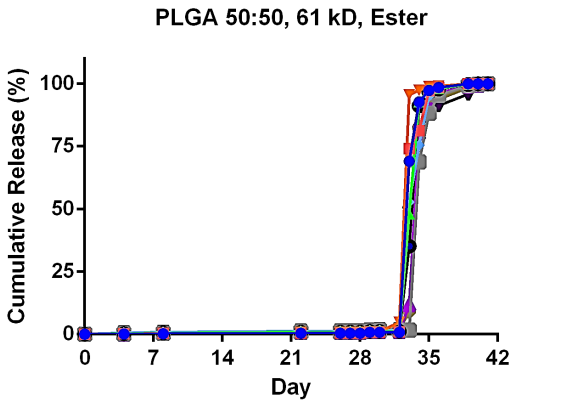
# Particle Base Geometries

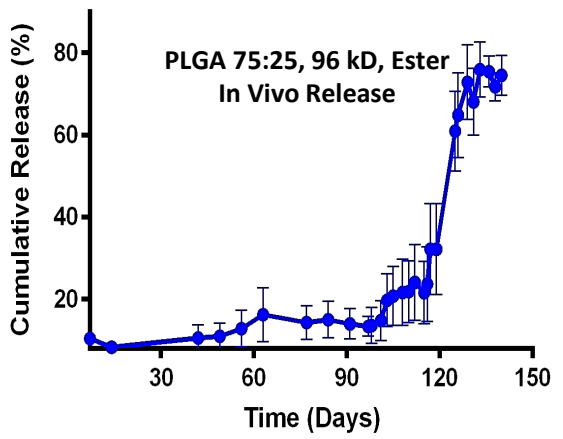


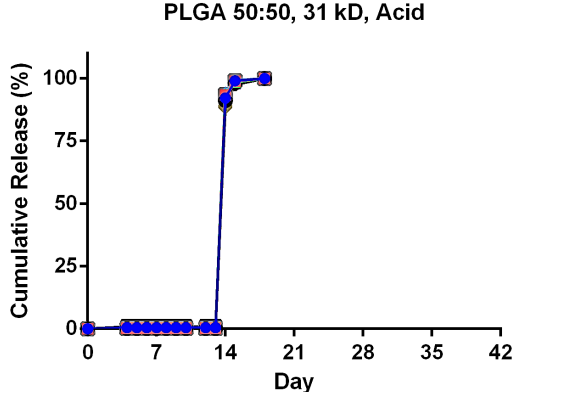

Scale bar = 500 μm

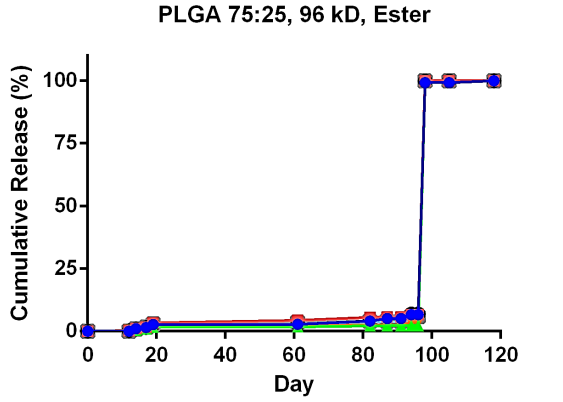
# Core-shell kinetic library

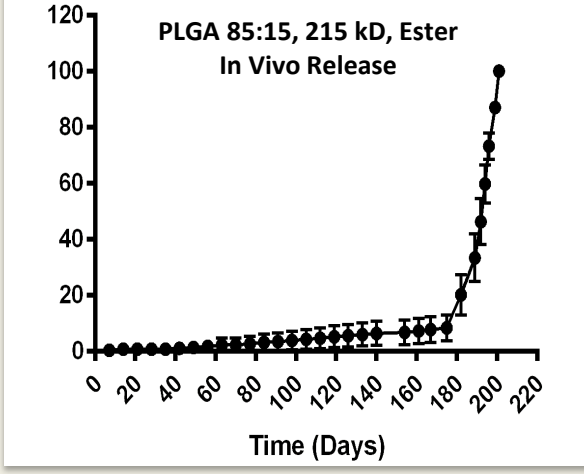


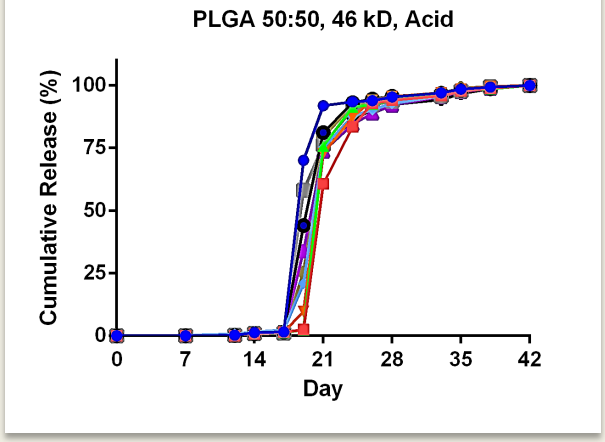



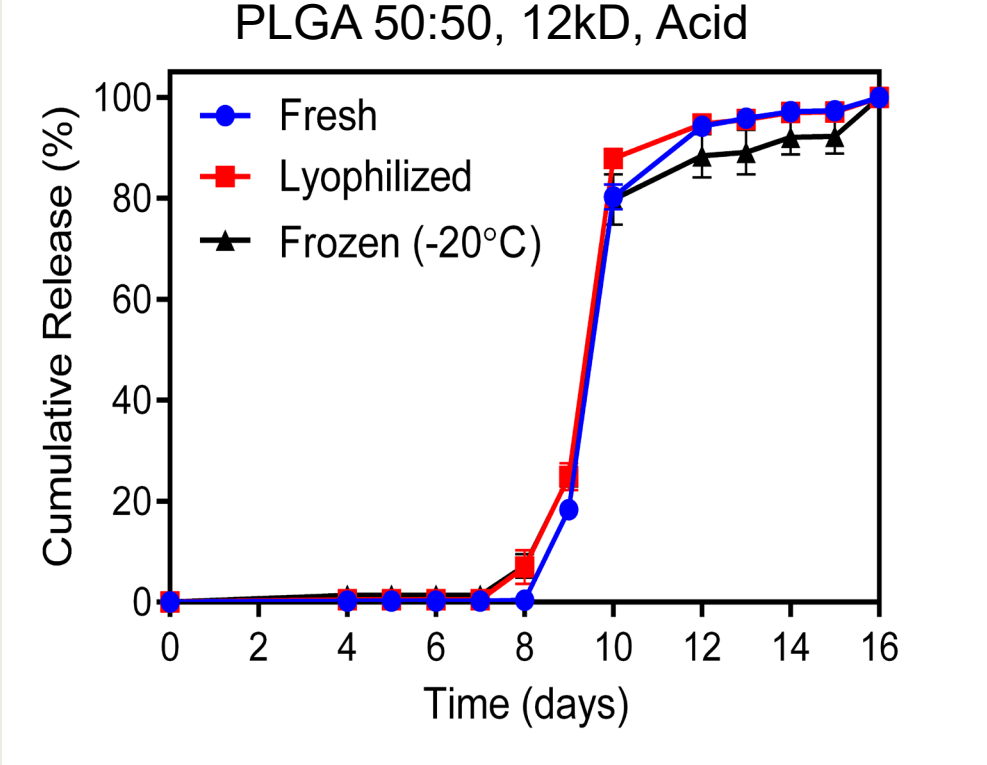




**Single-injection vaccination concept and release from SEAL-fabricated PLGA microparticles. A discrete, delayed pulse of antigen release to mimic current bolus vaccination regimens.**

from McHugh et al., Science 2017

# Core-shell particle stability

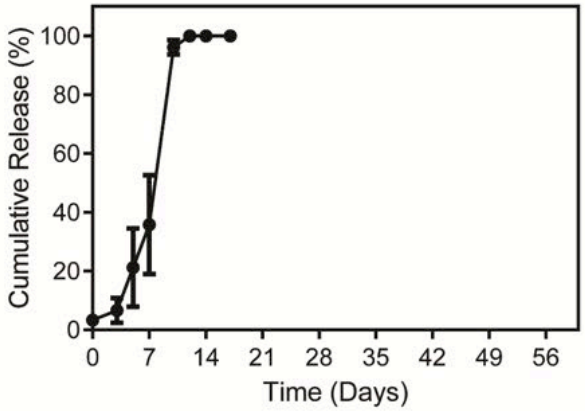
Release kinetics are unaltered by lyophilization or freezing at -20°C.

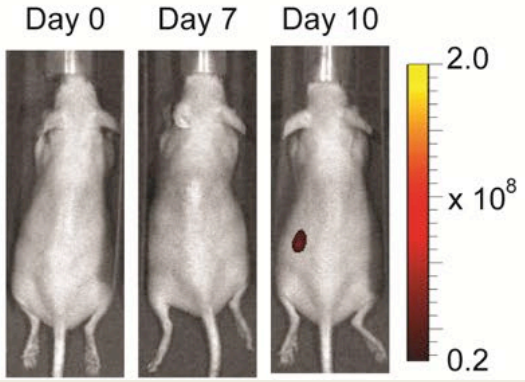


# In Vivo Release Kinetics

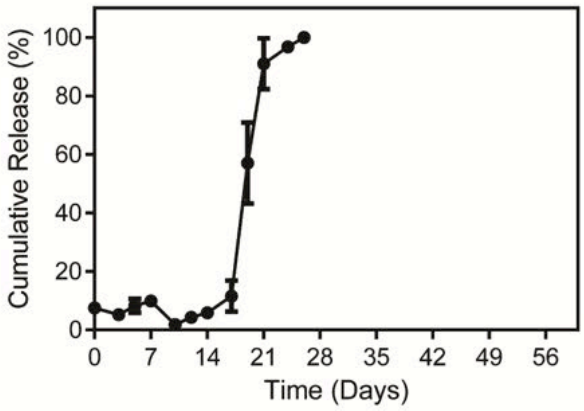
- In vivo kinetics were studied using IVIS imaging of particles loaded with AlexaFluor 680-BSA in SKH1-E mice
- No fluorescent before release, but a strong signal after release
- Delay in release is similar in vitro & in vivo

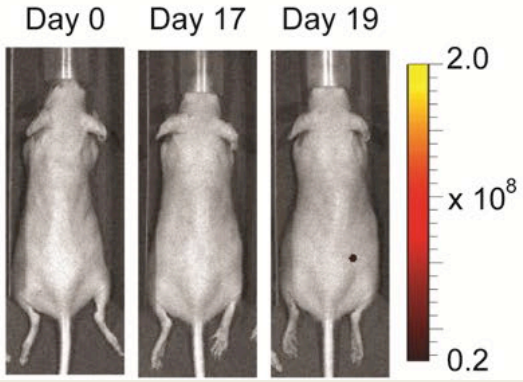
PLGA 50:50, 12kD, Acid



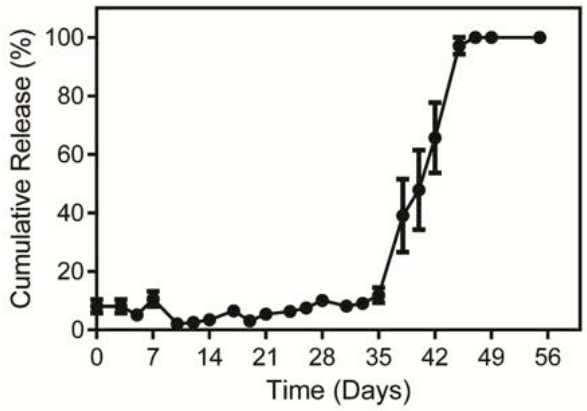



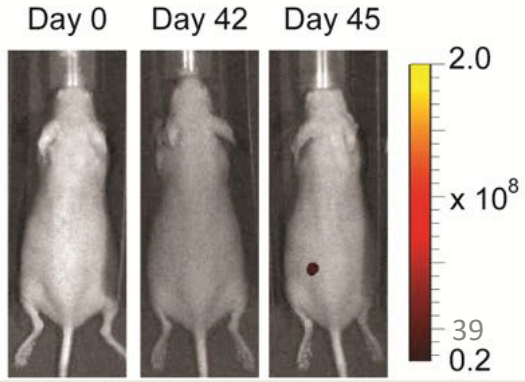

PLGA 50:50, 46kD, Acid



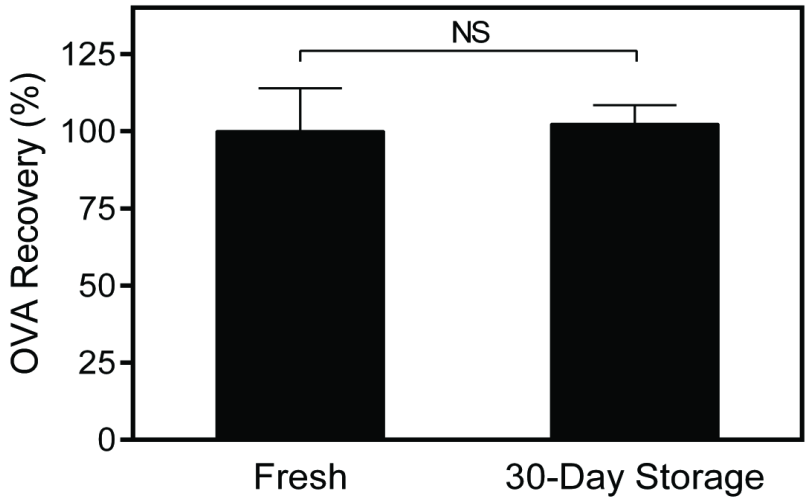

PLGA 50:50, 61kD, Ester



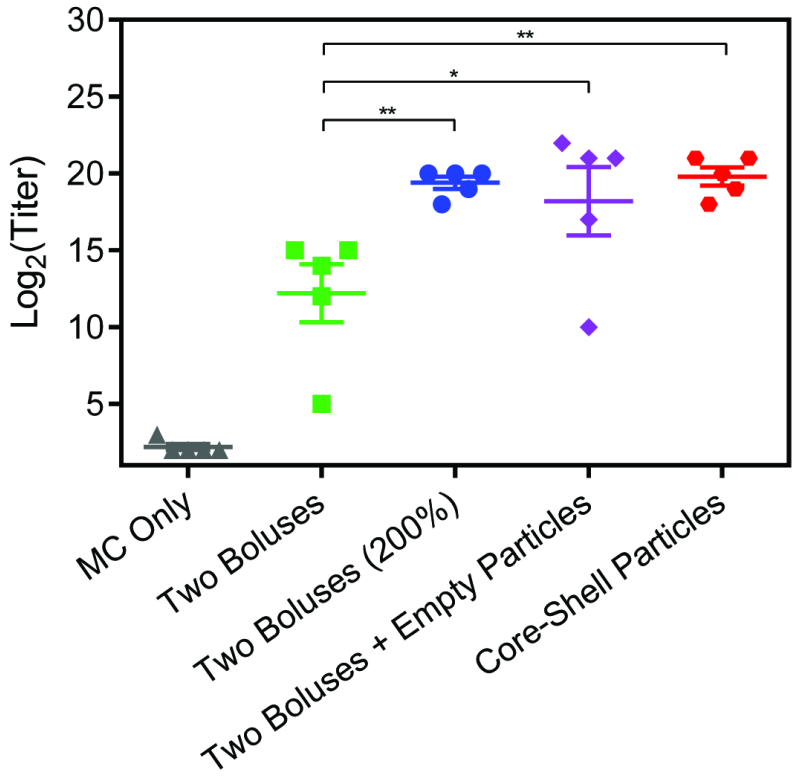
# OVA core shell particles

## *stability and vaccination*



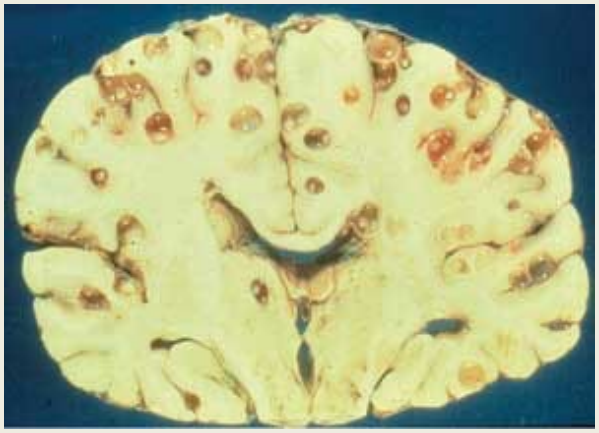

*particles stored desiccated for 30 days at 4°C*

PLGA 50:50, 61kD, Ester



# Neurocysticercosis

- Infection with the larval stage of a tapeworm parasite, **Taenia solium**, is the most frequent cause of preventable epilepsy in the developing world.
- The disease caused by this parasite (cysticercosis, or neurocysticercosis when the cysts are in the brain) is on WHO's list of Neglected Tropical Diseases (NTDs).
- The International Taskforce for Disease Eradication constituted by the Carter Centre includes cysticercosis as one of the few diseases that have a realistic potential to be eradicated.



http://altered-states.net/barry/newsletter387/

# T. Solium vaccine

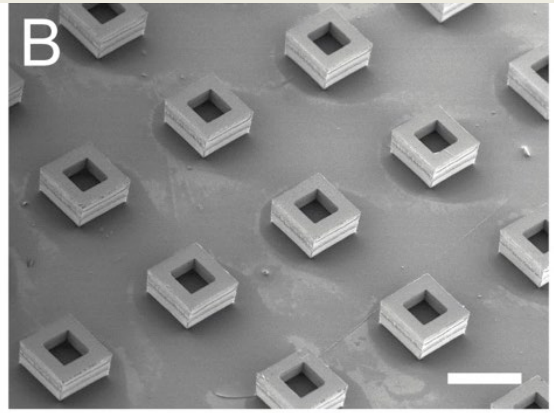
*Marshall Lightowlers, Univ. of Melbourne*

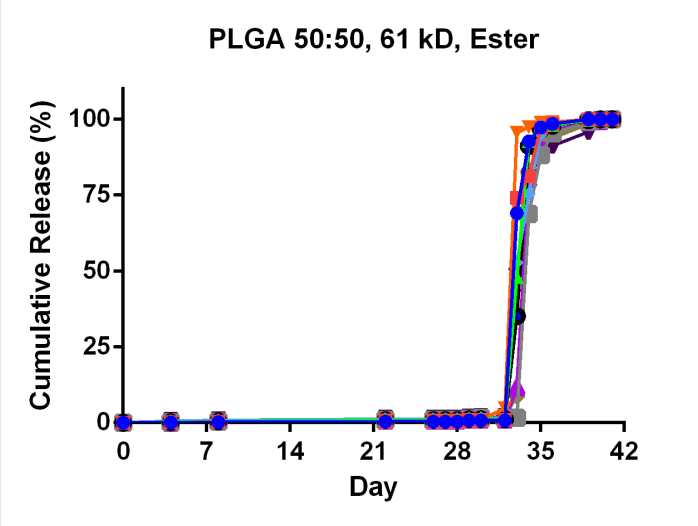
- T. solium vaccine targets pigs because that will indirectly prevent transmission to humans
- The vaccine incorporates 200µg Pichia or E. coli expressed protein plus a conventional veterinary adjuvant (Quil A or Montanide oil)
- The protective mechanism is vaccine-induced IgG and complement-mediated lysis of the early developing parasite
- Two injections about a month apart are required to get a protective response; however, implementing this schedule is likely infeasible
- One-time vaccination may be more readily implemented

# Single Injection T. Solium vaccine

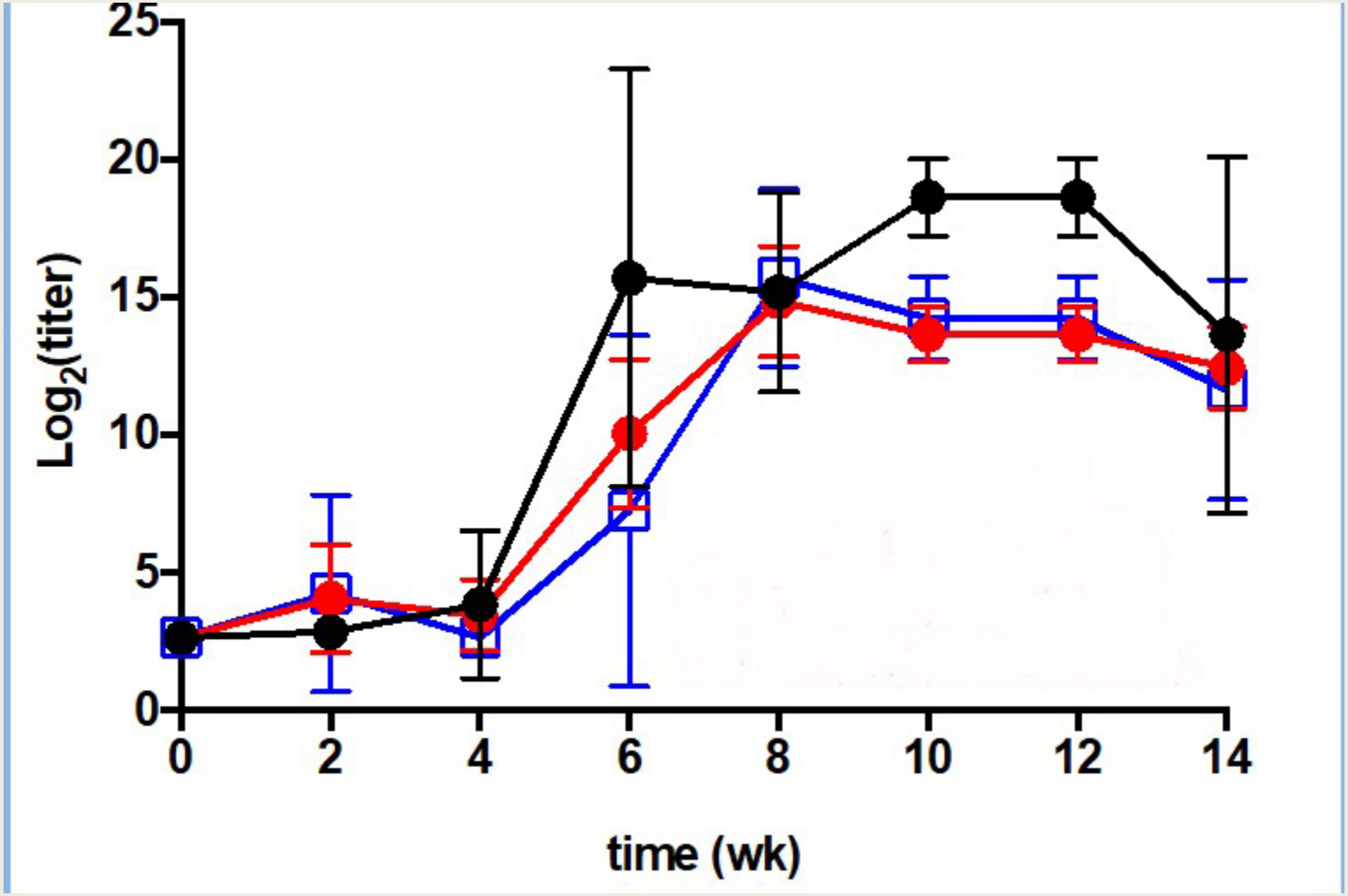
- A delivery system that requires only one injection would greatly increase the potential for this vaccine to have a global impact.

- Ideal release kinetics would be time 0, time 1 month

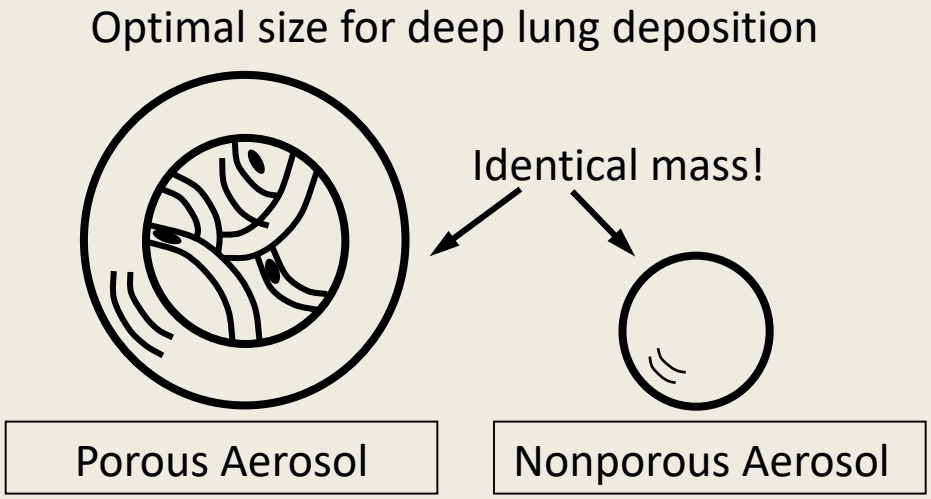


# TSOL18-specific IgG

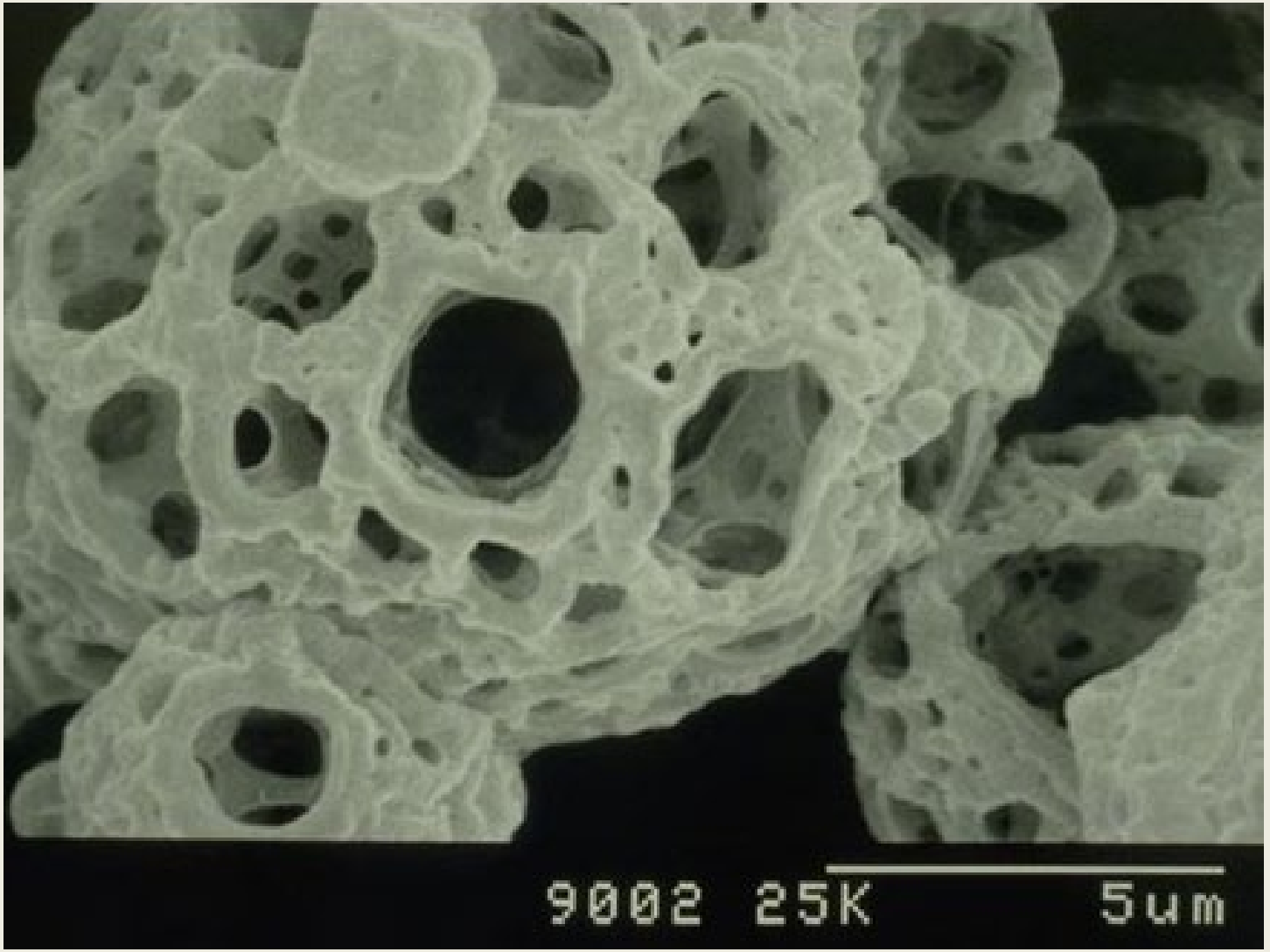


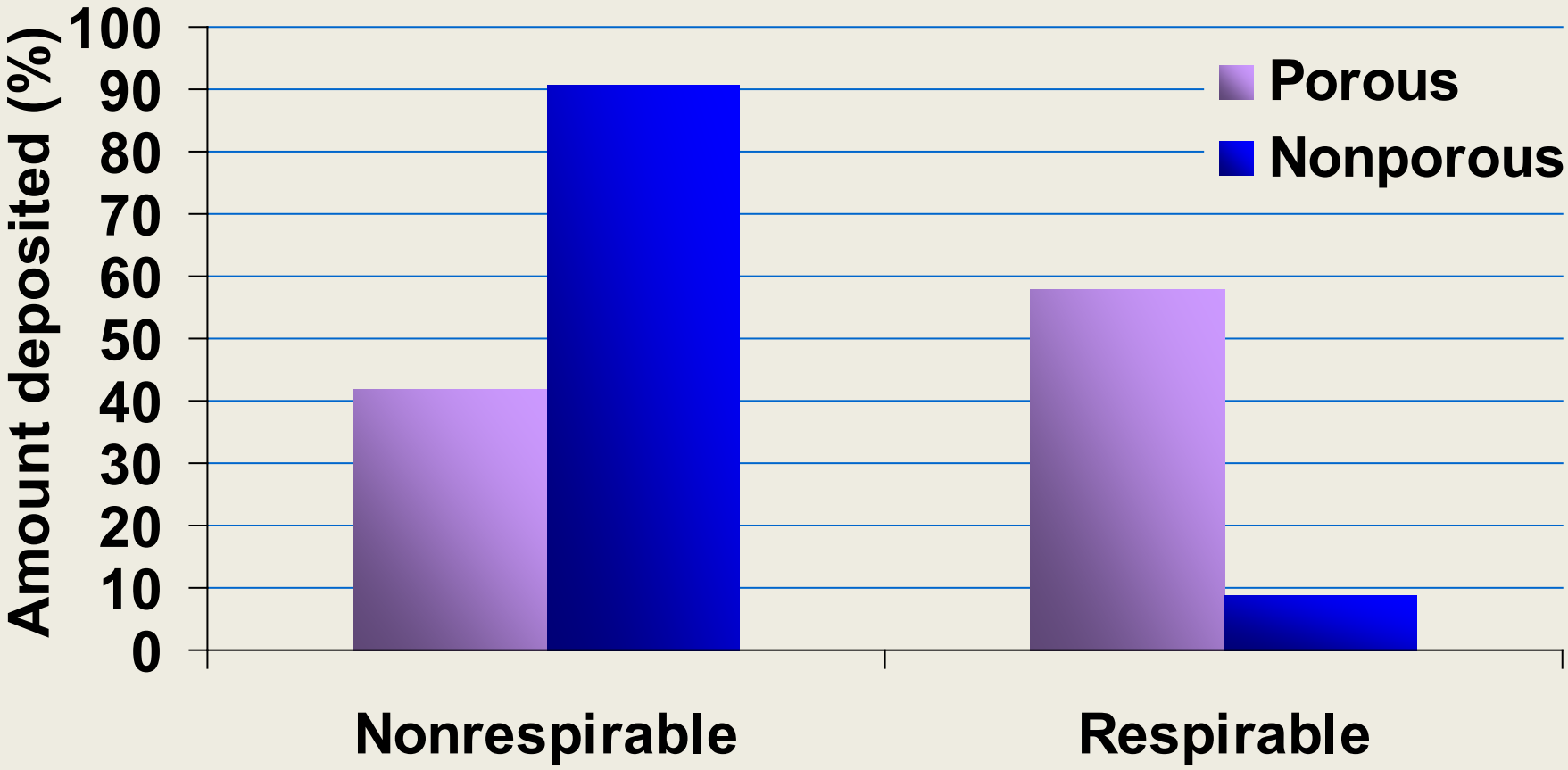
# The concept of porous aerosols for inhalation therapy

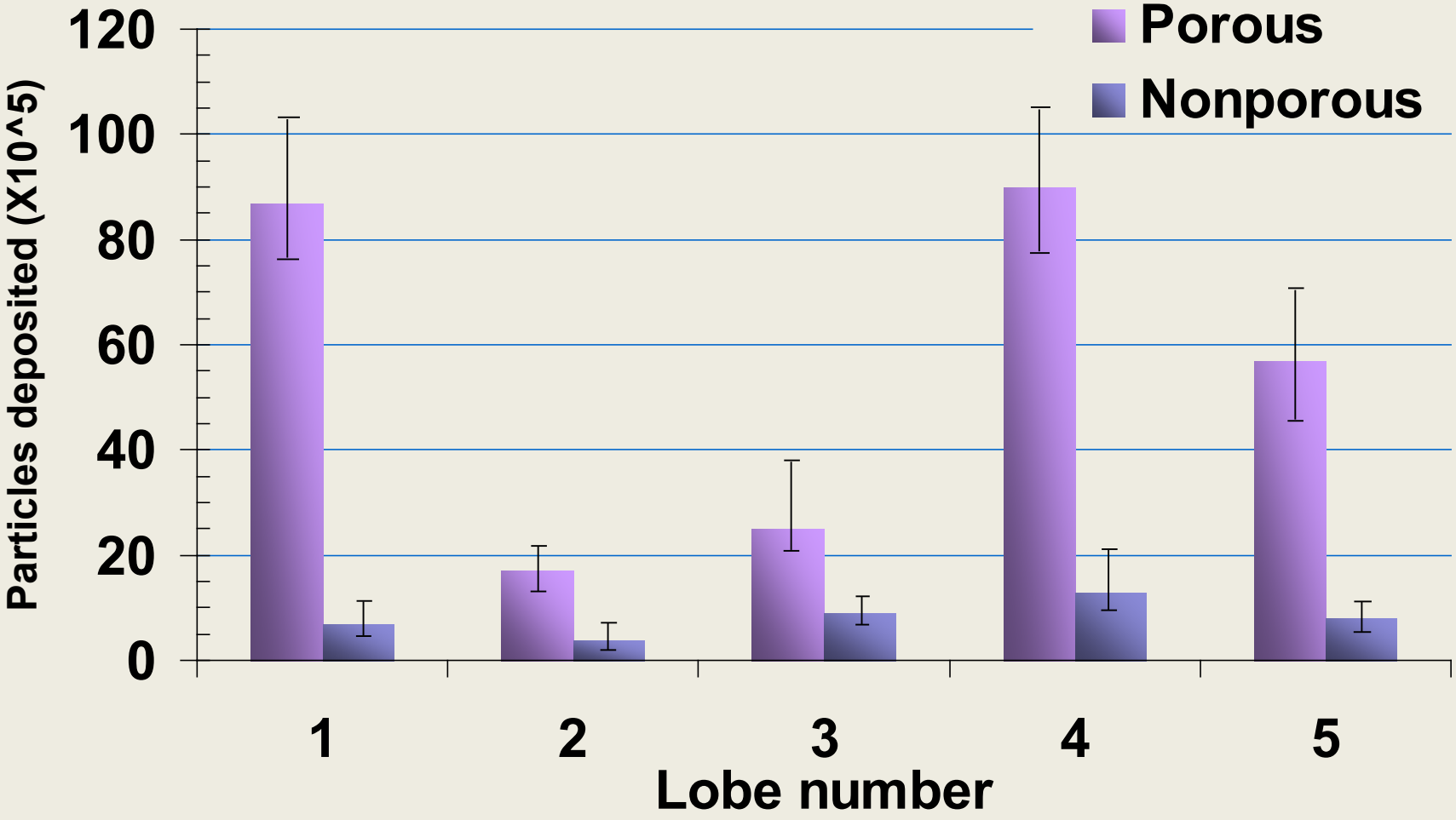



Advantages of large size for therapeutic aerosols:

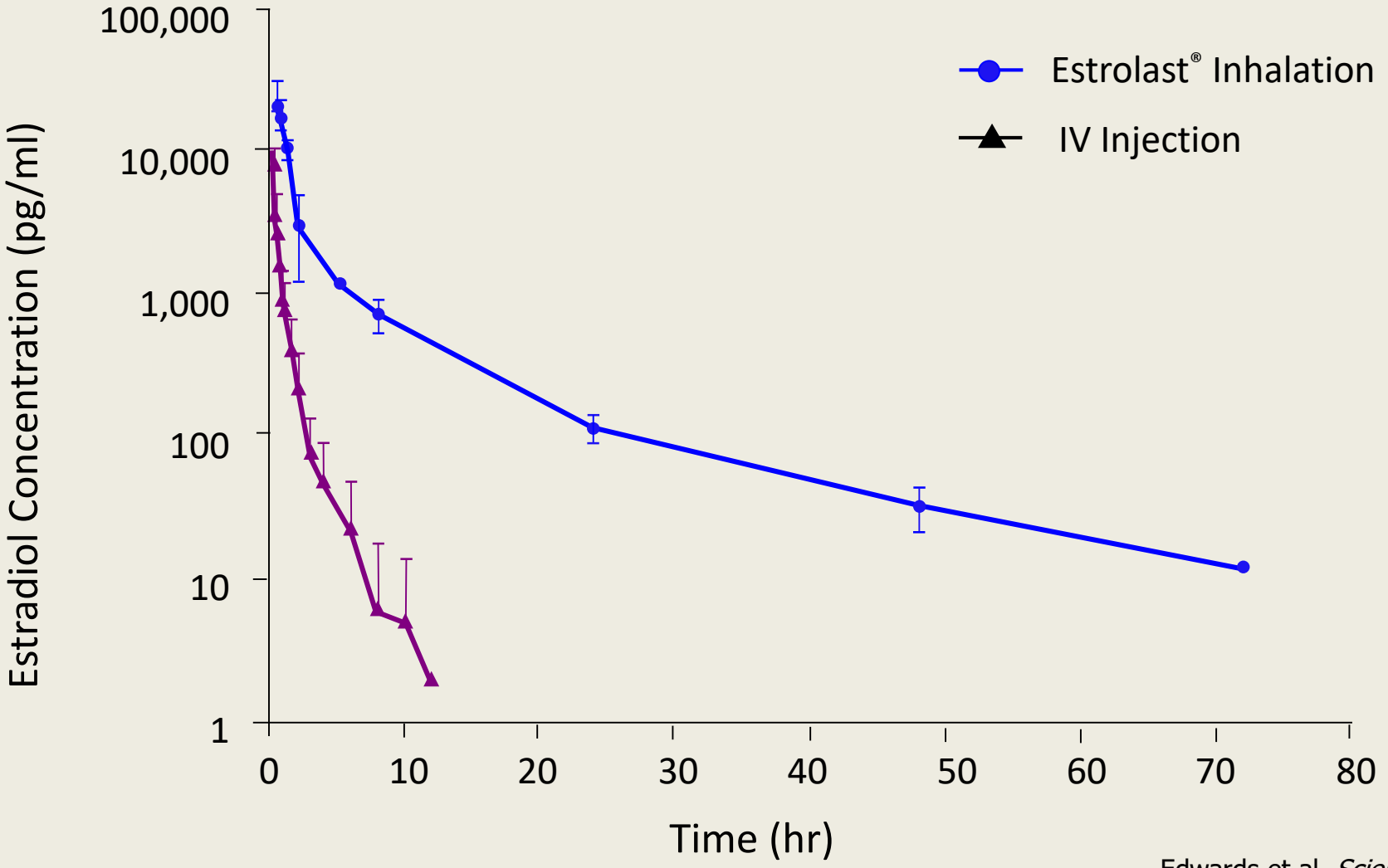
- Easier aerosolization and flowability
- Less prone to phagocytosis
- Enables delivery of large masses/payloads (critical for LS delivery)


9002 25K
5um


Amount deposited (%)
100
90
80
70
60
50
40
30
20
10
0
Porous
Nonporous
Nonrespirable
Respirable


Porous
Nonporous
Particles deposited (X10^5)
120
100
80
60
40
20
0
1
2
3
4
5
Lobe number

# Pharmacokinetic profile of estrolast



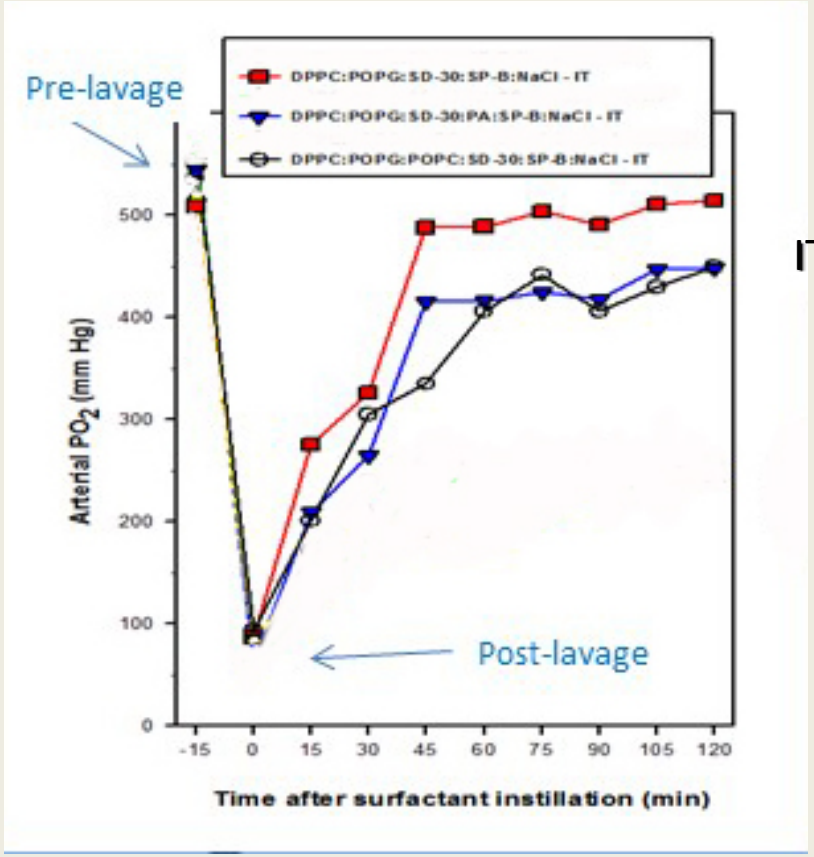

Edwards et al, *Science*, 1997

# INBRIJA (levodopa inhalation powder)


™Acorda Therapeutics, Inc.

- Rabbit lungs were lavaged to remove endogenous LS followed by DP LS powder delivery and subsequent measurement of arterial $PaO_2$ and lung compliance

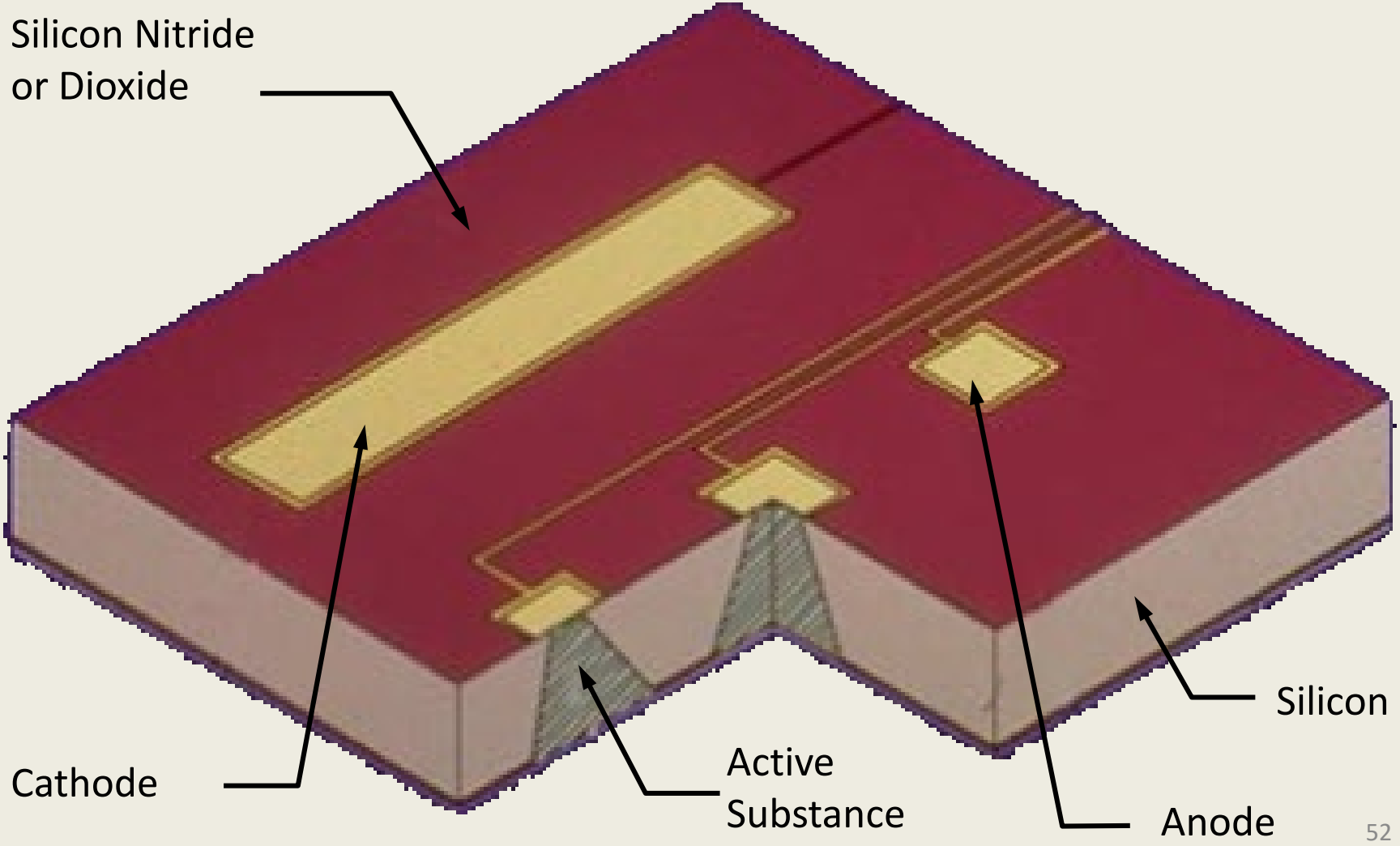
- DP LS powders delivered intratracheally (3) displayed excellent results with respect to arterial $PaO_2$ and lung compliance recovery post-lavage

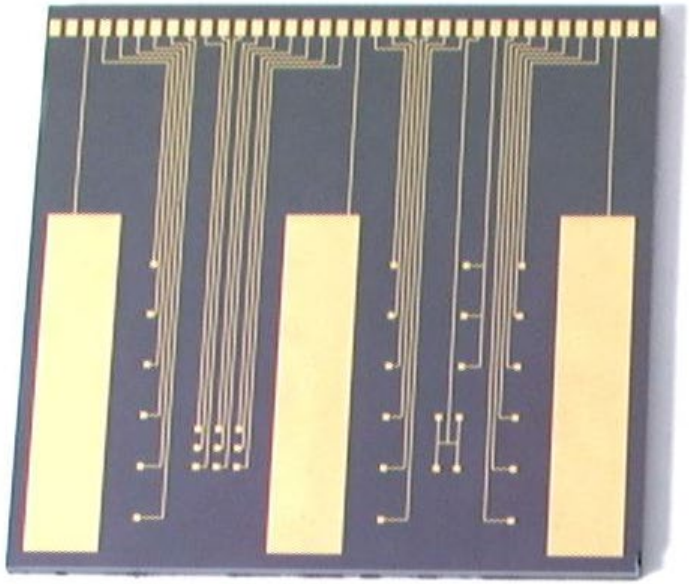


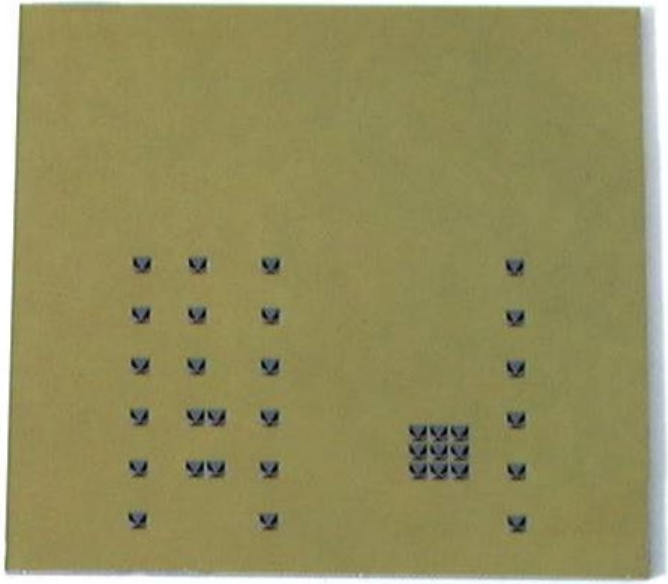

IT

Arterial $PaO_2$ recovery results seen for the lead and backup formulations delivered intratracheally and via nasal CPAP after lung lavage

# Prototype device



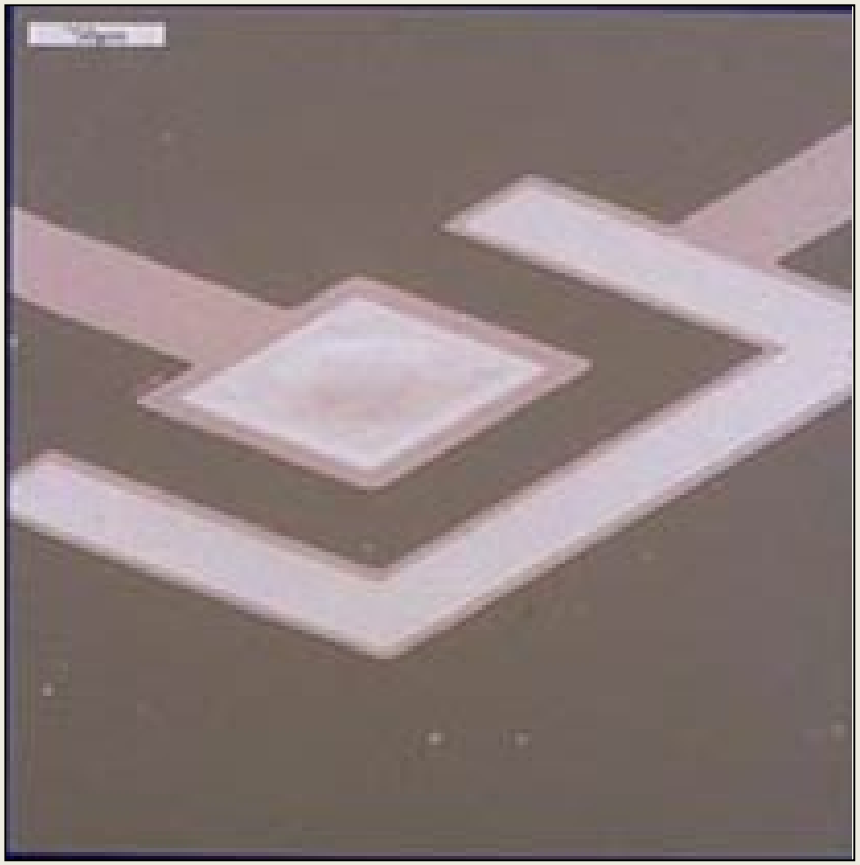




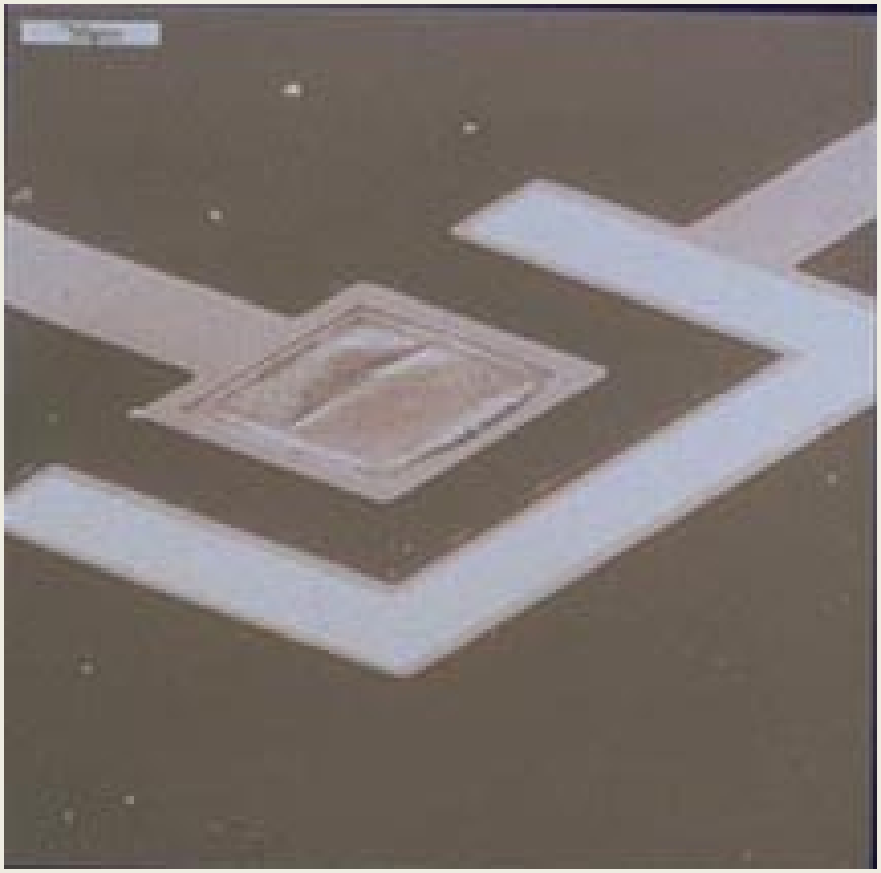

LIBERTY
IN GOD
WE TRUST
1997
P

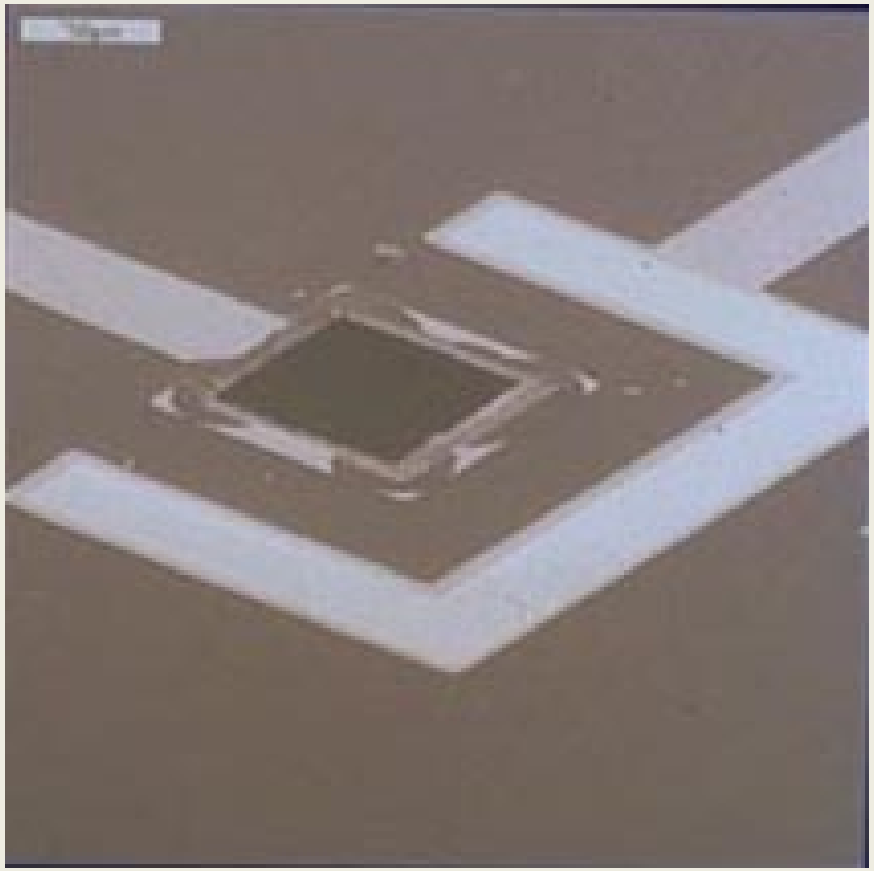
# Reservoir activation

SEM of a reservoir – electrode system before application of an electric potential



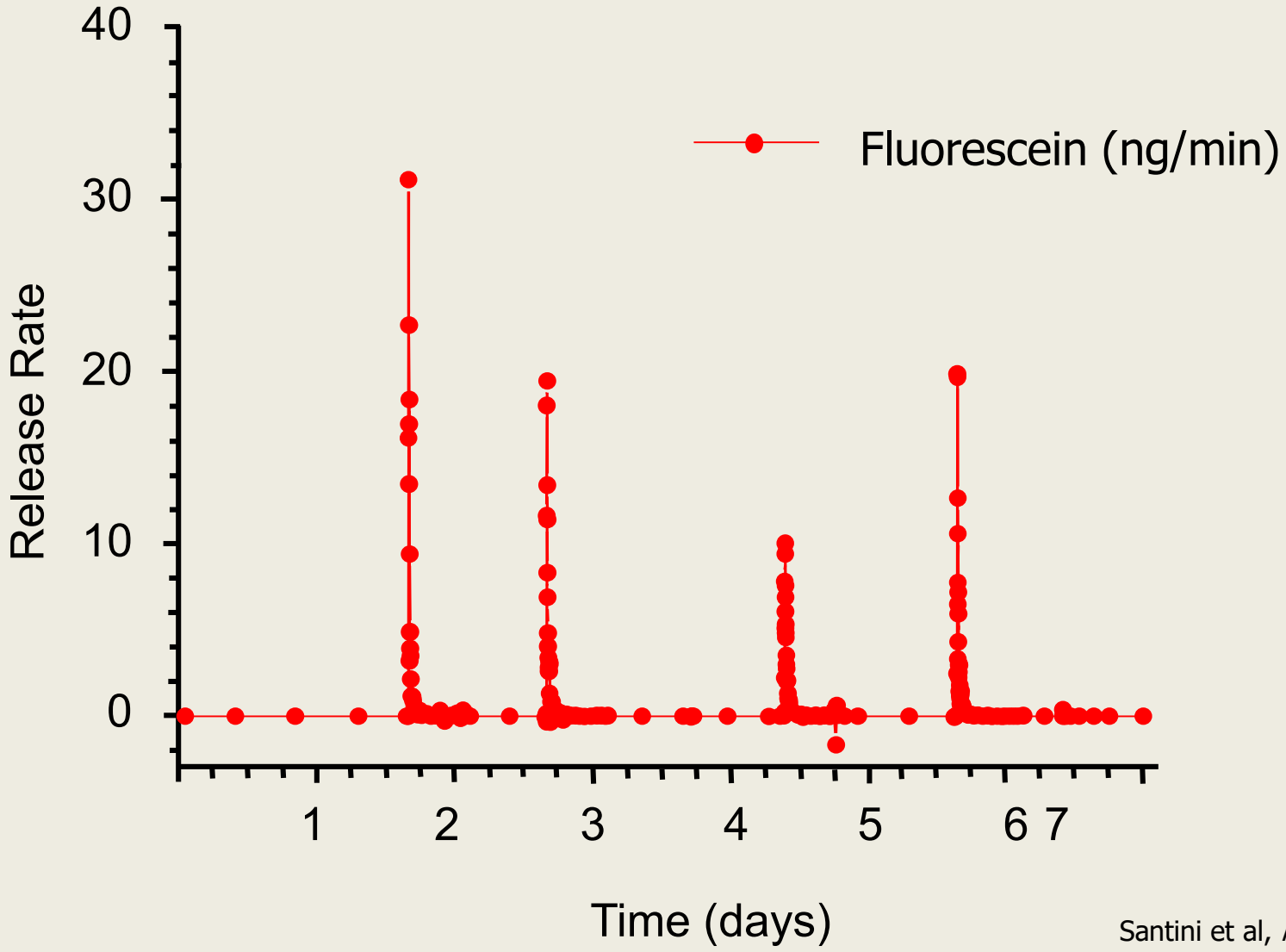
# Reservoir activation





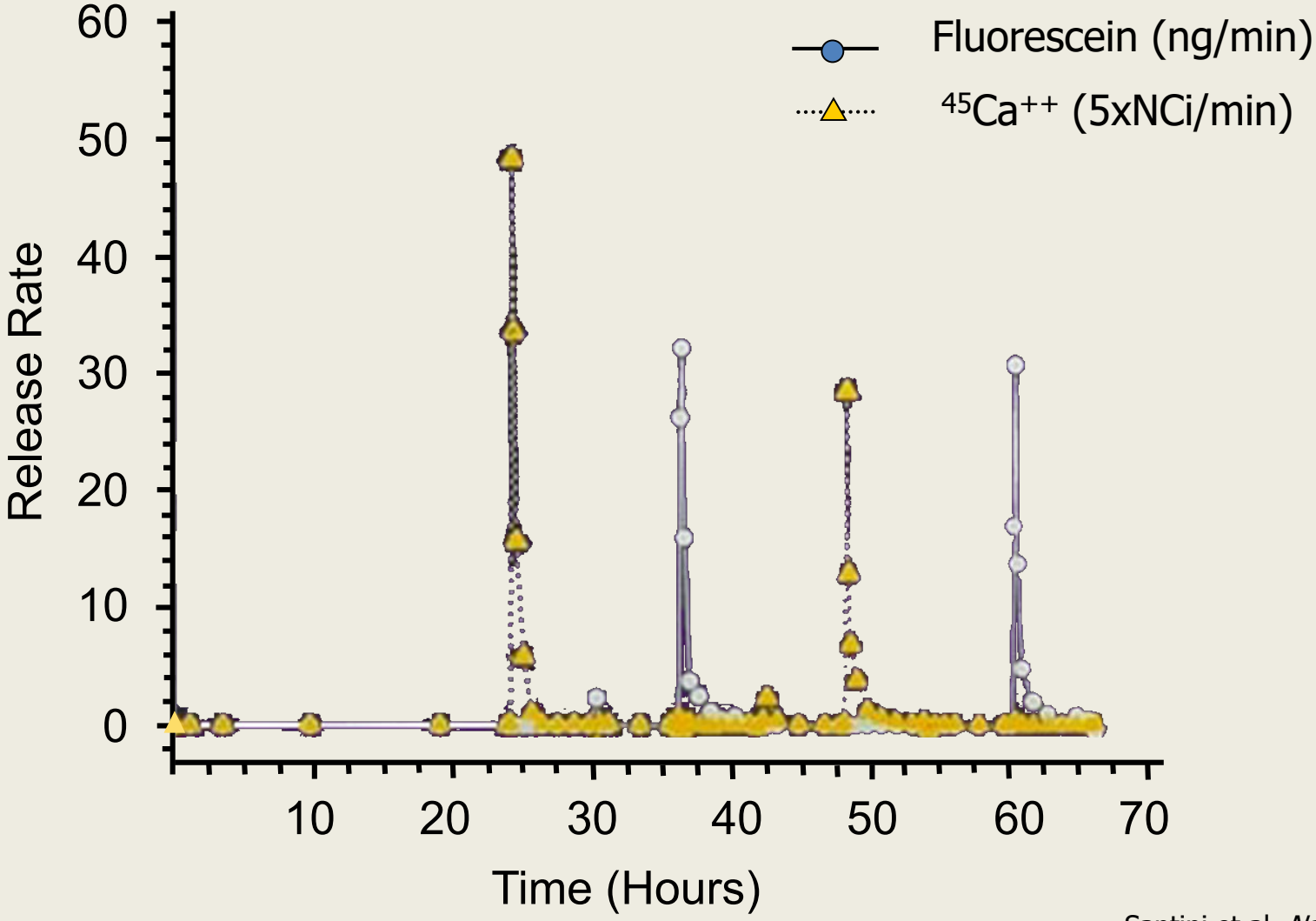
SEMs taken after application of 1.04 volts vs. SCE in PBS

# Single compound release




Santini et al, *Nature*, 1999

# Multiple compound release




Santini et al, *Nature*, 1999

# Clinical trial

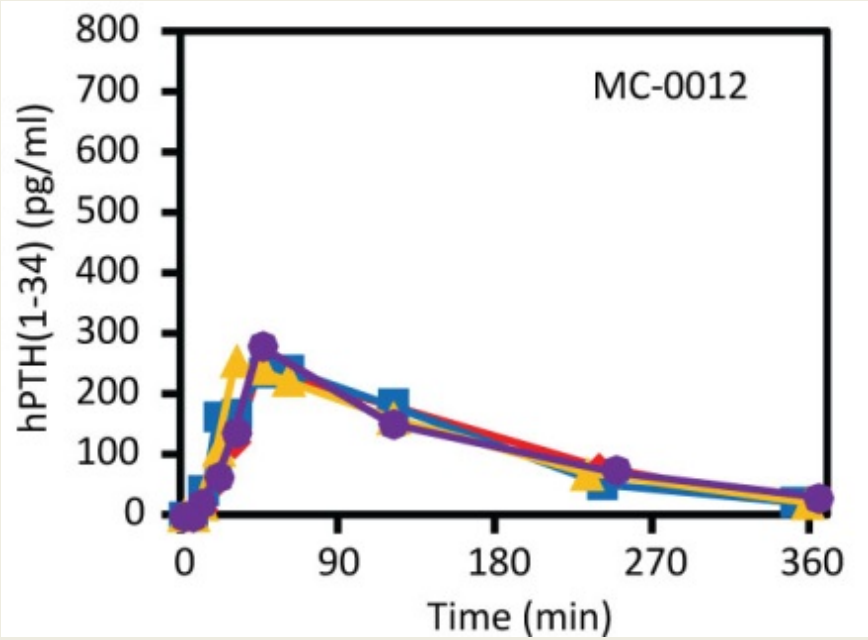
- Chips are communicated with over a special frequency called the Medical Implant Communications Service Band, approved by both the FCC and the FDA.

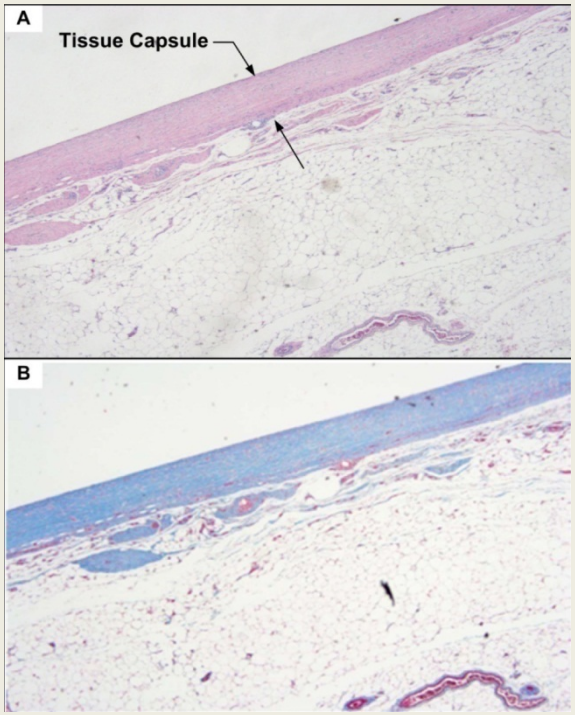
- A patient or doctor enters a special computer code to administer or change the dose.

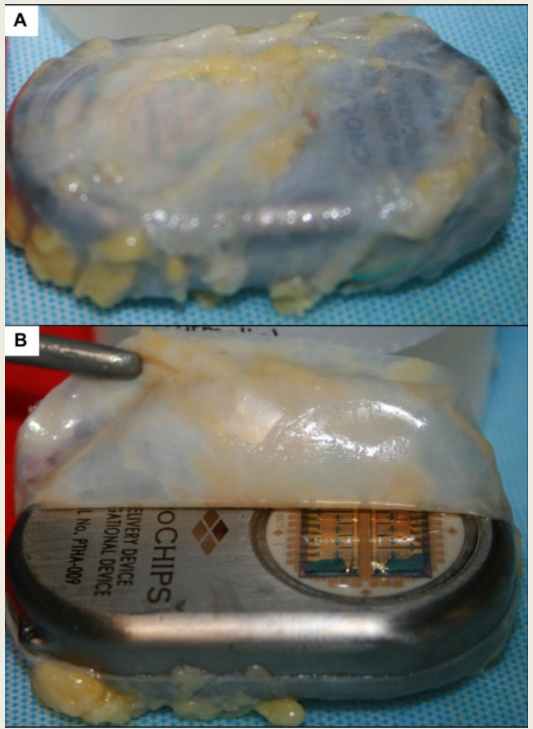
- Bidirectional communications link between the chip and receiver enables the upload of status information, including confirmation of dose delivery, battery life, etc.

# Clinical trial

- 8 patients
- PTH (compliance with injections is 25%)
- Small office procedure to implant
- Some pharmacokinetics (less variability) and Ca, PINP, CTX measures as daily injections


MC-0012
hPTH(1-34) (pg/ml)
800
700
600
500
400
300
200
100
0
0
90
180
270
360
Time (min)

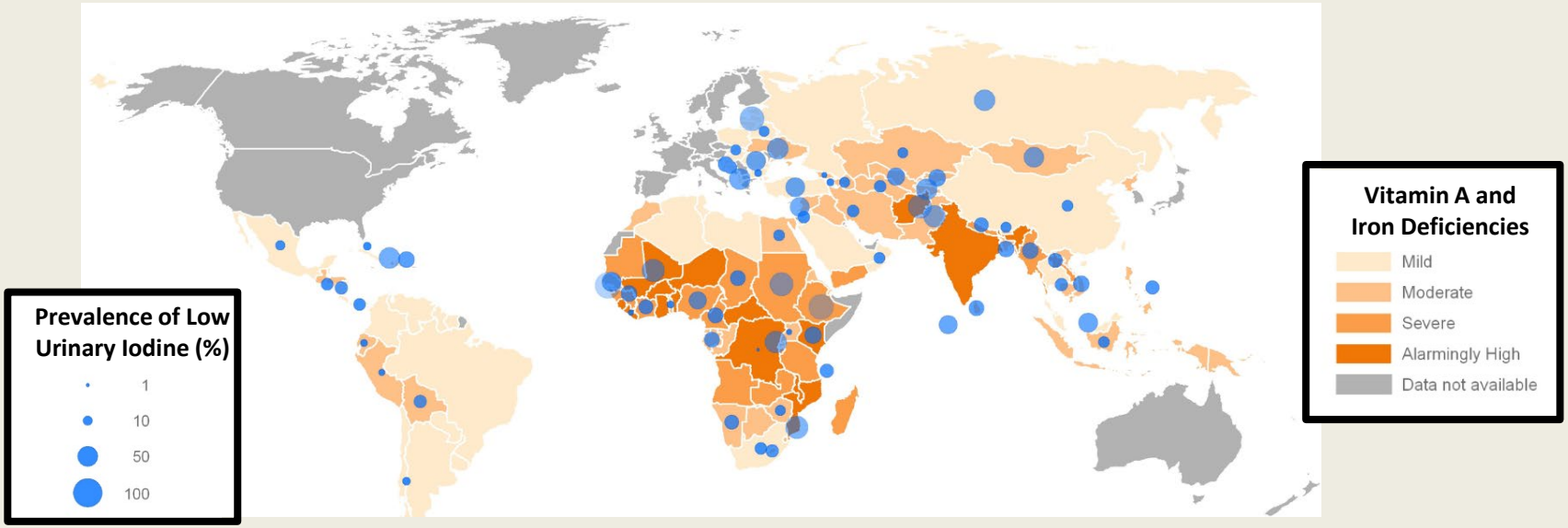

A
Tissue Capsule
B


A
B

# Gates Foundation grant

- Grant: December 2012 through May 2019
- Purpose: to develop a personal fertility control system with emphasis for use by women living in Developing World countries as a means to effectively plan their families

# More Than 2 Billion People Suffer from Micronutrient (MN) Deficiencies Worldwide

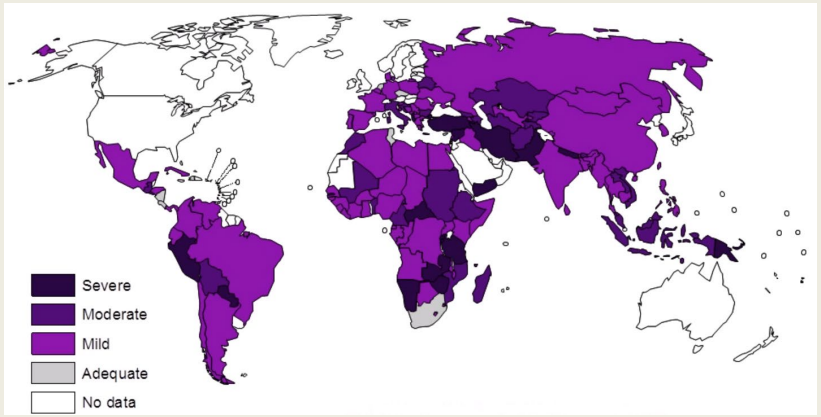



MN deficiencies lead to impaired physical and cognitive development, increased morbidity risks, reduced work productivity, and are responsible for 20% of all maternal deaths

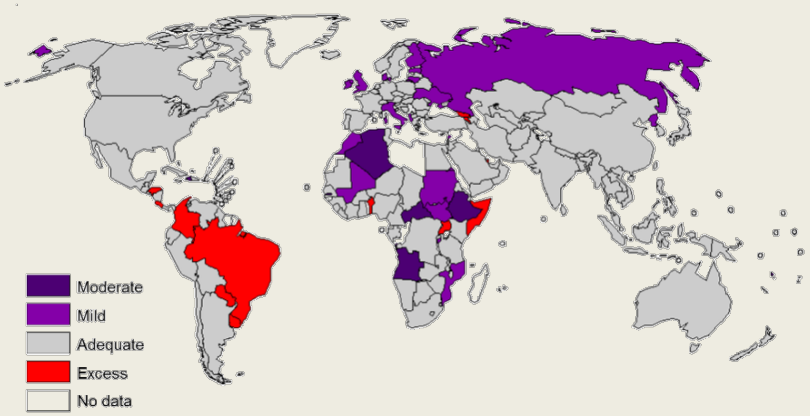
*Black et al, "The Global Hidden Hunger Indices and Maps: An Advocacy Tool for Action", PLoS One (http://www.ncbi.nlm.nih.gov/pmc/articles/PMC3680387/)*

# Micronutrient Fortification Works

**In 1993, 110 countries were iodine deficient…**




**…versus 2015, when that number was only 25**




- Iodized-salt fortification was successful in reducing iodine deficiency
  - Program benefitted from harnessing a widely used vehicle (i.e., salt)
  - Relatively easy MN to address because it is relatively stable during storage and cooking
- Stabilization and mass fortification of other MNs is much more difficult
  - Iron and vitamin A easily oxidize and degrade, which limits their absorption

*Source: Iodine Global Network*. "Two decades of progress against iodine deficiency: 1993-2015". Oct 2015.

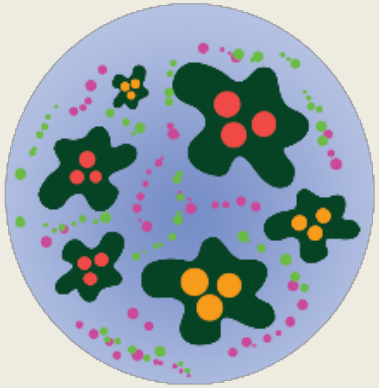
# The potential needs are HUGE

- 250 M preschool children suffer from vitamin A deficiency worldwide

- 40% of the world suffers from iron deficiency and anemia

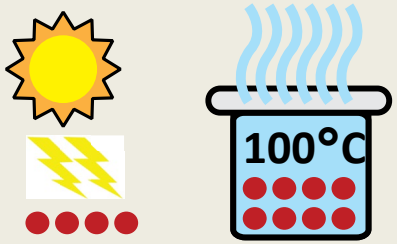
# Challenges of Omni-Fortification: Must be Addressed simultaneously

**1. Encapsulation**



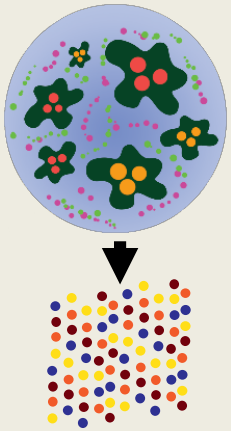
- Dispersion of MNs into distinct foods (salt, flour)
- Methods to co-encapsulate fat- and water-soluble MNs
- Interactions with other MNs, food…

**2. Stability**




- Cooking
  - Temperature degradation
  - Oxidation
- Storage
  - Light sensitivity
  - Humidity
- Organoleptic

**3. Ensuring Intestinal Absorption**



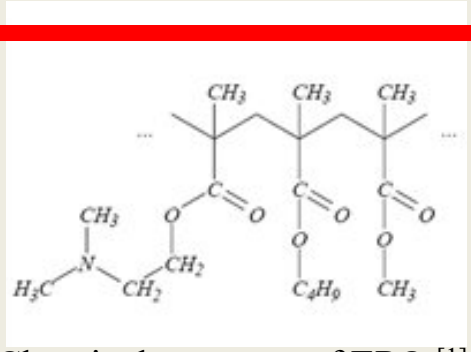
- Mediate MN-intestine interactions via burst release

# Polymer Jacket

## *Material Selection – Low pH Solubility*

~~Polyvinyl Acetate Pthalate (PVAP)~~
~~Acrylic Polymer~~
~~Methyl Acrylate-Methacrylic Acid Copolymers~~
~~Cellulose Acetate Succinate~~
~~Hydroxy Propyl Metyl Cellulose Phthalate~~
~~Hypromellose Acetate Succinate~~
**Methyl methacrylate-methacrylic acid copolymers (EPO)**
~~Acryl EZE~~
~~KADCOAT E100-40~~
~~Sodium Alginate and Stearic Acid~~
~~Hypromellose Phthalate~~
~~Cellulose Acetate Phthalate~~
~~Polymethacrylates~~
~~Shellac~~
~~Sureteric~~
~~Opadry~~
~~Nutrateric II~~
~~Chitosan~~

*Almost all the commercialized tablet coatings are enteric (dissolve above pH 5), which are designed to bypass the stomach rather than dissolve them.*

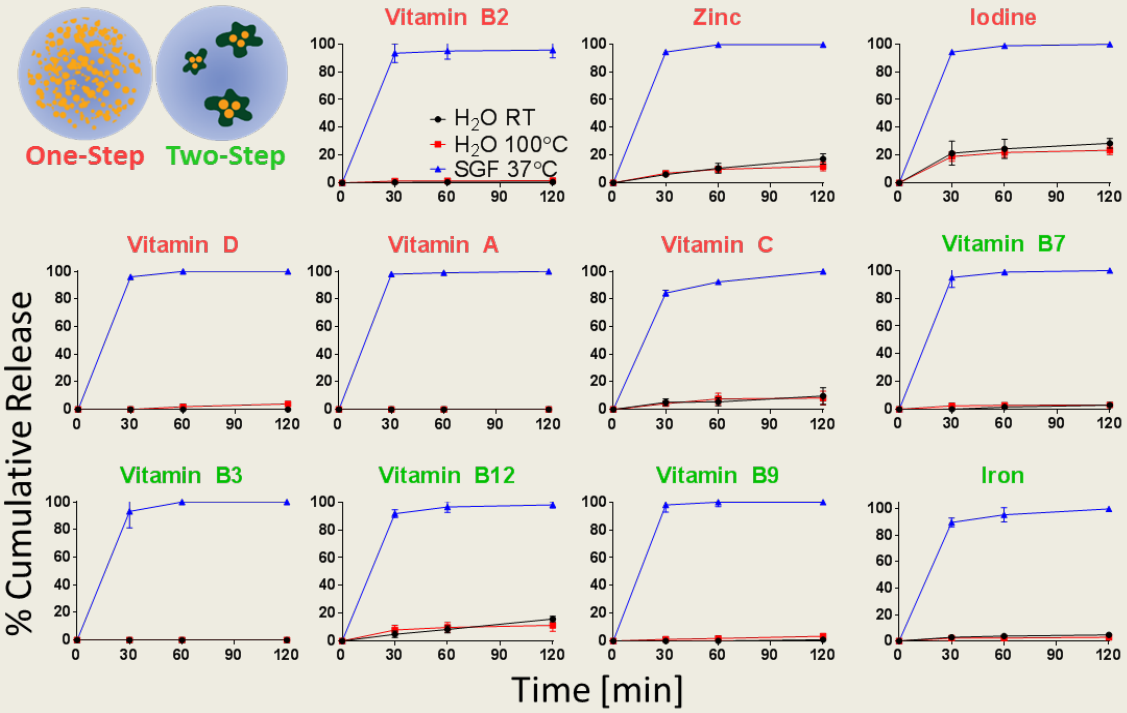


Chemical structure of EPO [1]

Basic Methacrylate Copolymer (EPO) was used as the polymeric matrix. It is a cationic polymer which can be dissolved at low pH (pH<5).

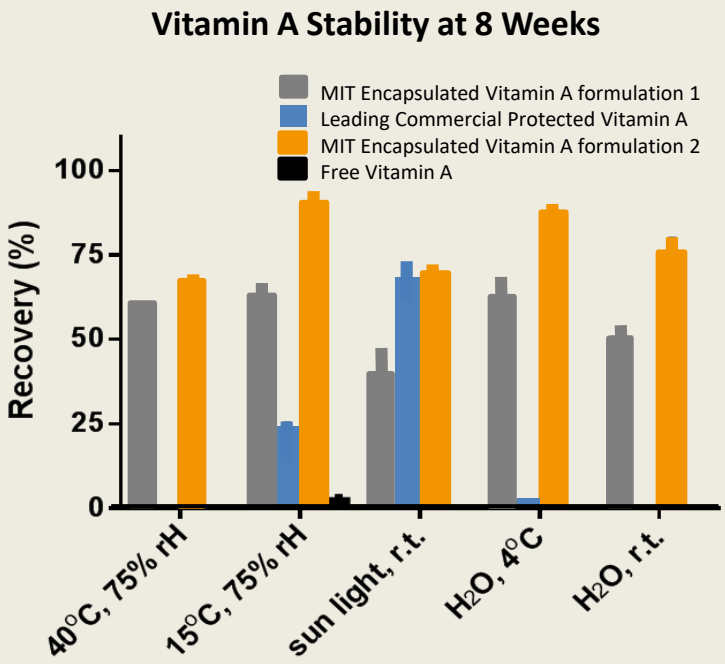
[1] Image source: www.evonik.com

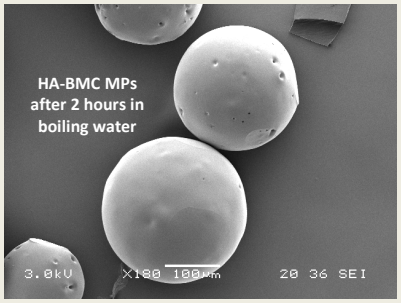
# 11 Heat-Stable Micronutrient Formulations Developed

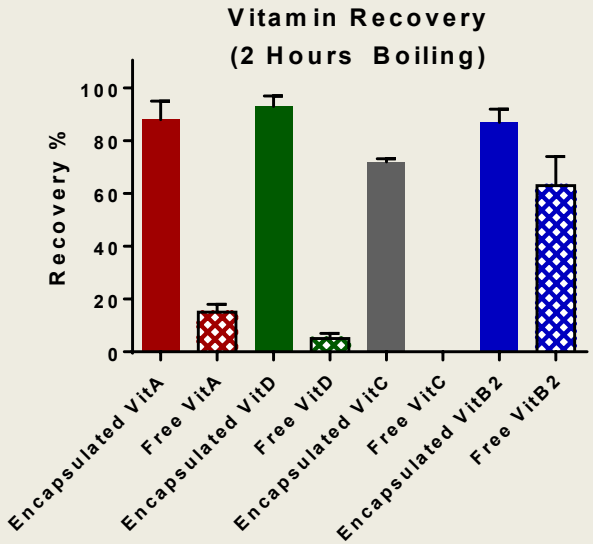



- All based on basic methacrylate copolymer (BMC) encapsulation
- All demonstrate stability in room temperature and 100°C water
- All rapidly dissolve in simulated gastric fluid (SGF)

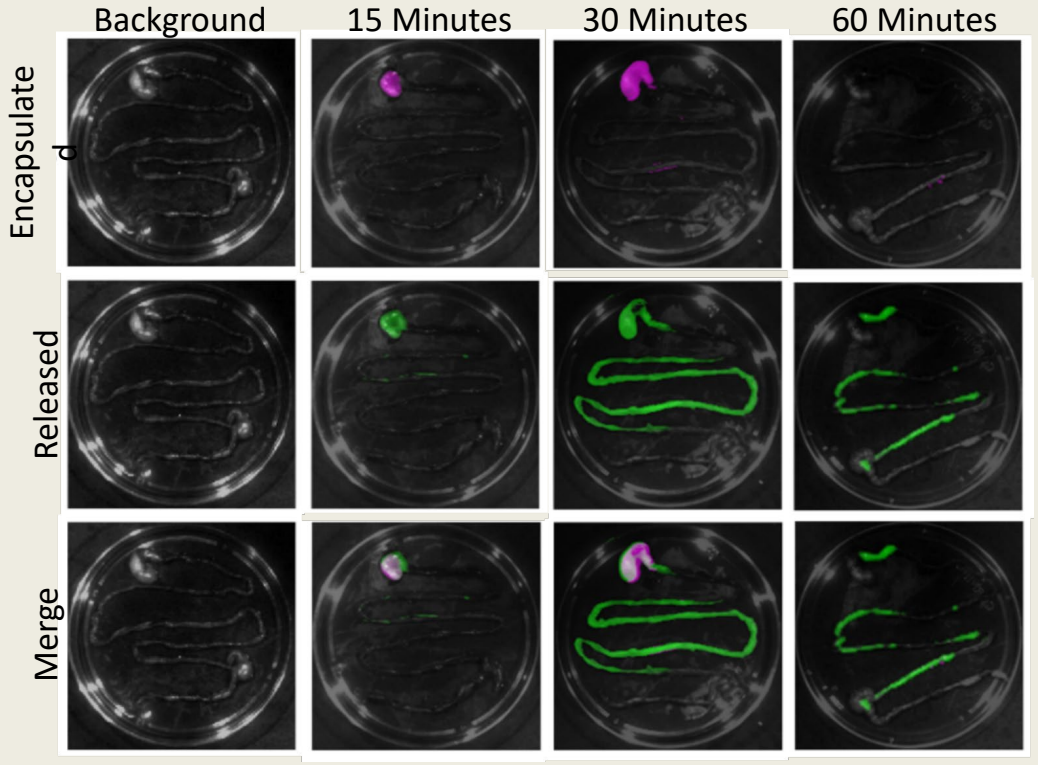
# Particles Are Designed to Withstand Storage and Cooking Conditions



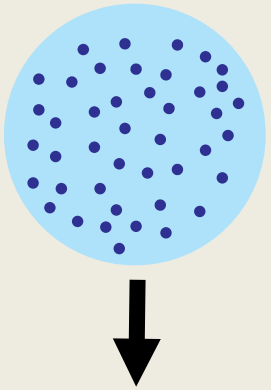



# Burst Release in Stomach Conditions to Enable MN Absorption



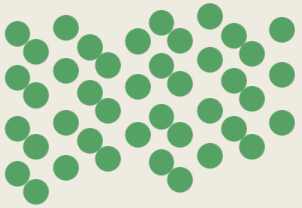

**Purple**:

Dye in Microspheres



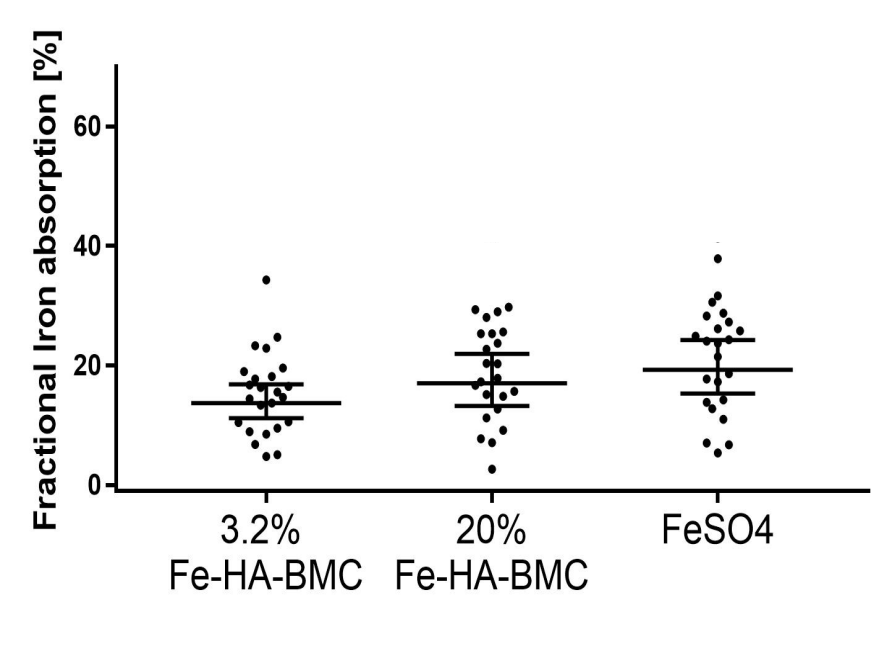
**Green**:

Released Dye



***CONFIDENTIAL***

# Clinical Trial: Encapsulated versus Free Iron




- 89% in Human Trials

# Taste/Appearance (Vitamin A/Iron)

- In our bread, other foods

- No detectable taste or color change

# Positive Response from JECFA Paves the Path for Codex Approval

Food and Agriculture Organization of the United Nations

World Health Organization

**JOINT FAO/WHO EXPERT COMMITTEE ON FOOD ADDITIVES**
**Eight-sixth meeting**
**Geneva, 12–21 June 2018**

**SUMMARY AND CONCLUSIONS**
*Issued 3 July 2018*

***"The use of BMC… is not of safety concern when the food additive is used as a coating or glazing agent for… micronutrient encapsulation for food fortification"***

***Food additives evaluated toxicologically and assessed for dietary exposure***

| Food additive | Specifications | Acceptable daily intakes (ADIs) and other toxicological and dietary exposure conclusions |
|---|---|---|
| Basic methacrylate copolymer (BMC) | N | **The Committee established an ADI "not specified" for basic methacrylate copolymer.**<br>The Committee concluded that the use of BMC that complies with the specifications established at the current meeting is not of safety concern when the food additive is used as a coating or glazing agent for solid food supplements and for foods for special medical purposes and micronutrient encapsulation for food fortification. The NOAELs for BMC ranged from 750-2000 mg/kg bw per day which were the highest doses tested.<br>The Committee evaluated exposure to BMC for the copolymer and its monomers (n-butyl methacrylate, 2-(dimethylamino)ethyl methacrylate and methyl methacrylate). Estimated exposures to BMC range from 3.0 to 135 mg/kg bw per day. The total monomeric content of BMC is less than 0.3%. The Committee concluded that the toxicological data on the residual monomers do not give rise to concerns when taking into account the low dietary exposures. |

- : no specifications prepared; N: new specifications; R: existing specifications revised; T: tentative specifications