Next generation bioresorbable injectable contraceptive implants

Rob Steendam

CRS Educational Workshop, July 11, 2022

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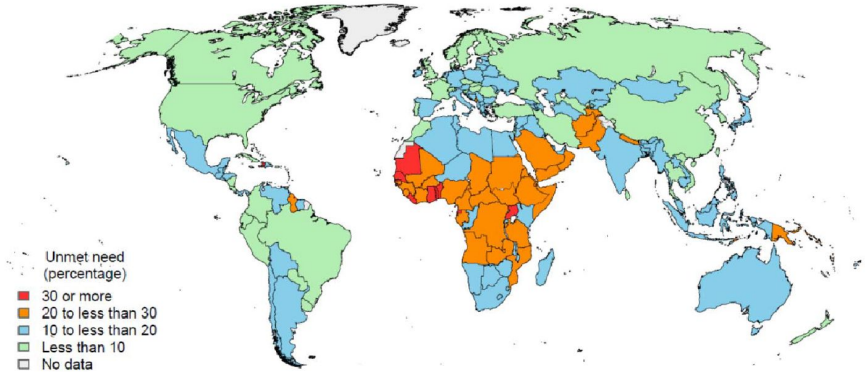
Contraception in lower and middle income countries (LMIC)



34% SAY THEY HAVE SEX INFREQUENTLY

24% are concerned about side effects or health risks

4% lack access

South America

1 in 10 women have unmet need for contraception

28% ARE CONCERNED ABOUT SIDE EFFECTS OR HEALTH RISKS

19% say they have sex infrequently

8% lack access

Africa

1 in 4 women have unmet need for contraception

31% SAY THEY HAVE SEX INFREQUENTLY

23% are concerned about side effects or health risks

6% lack access

Asia

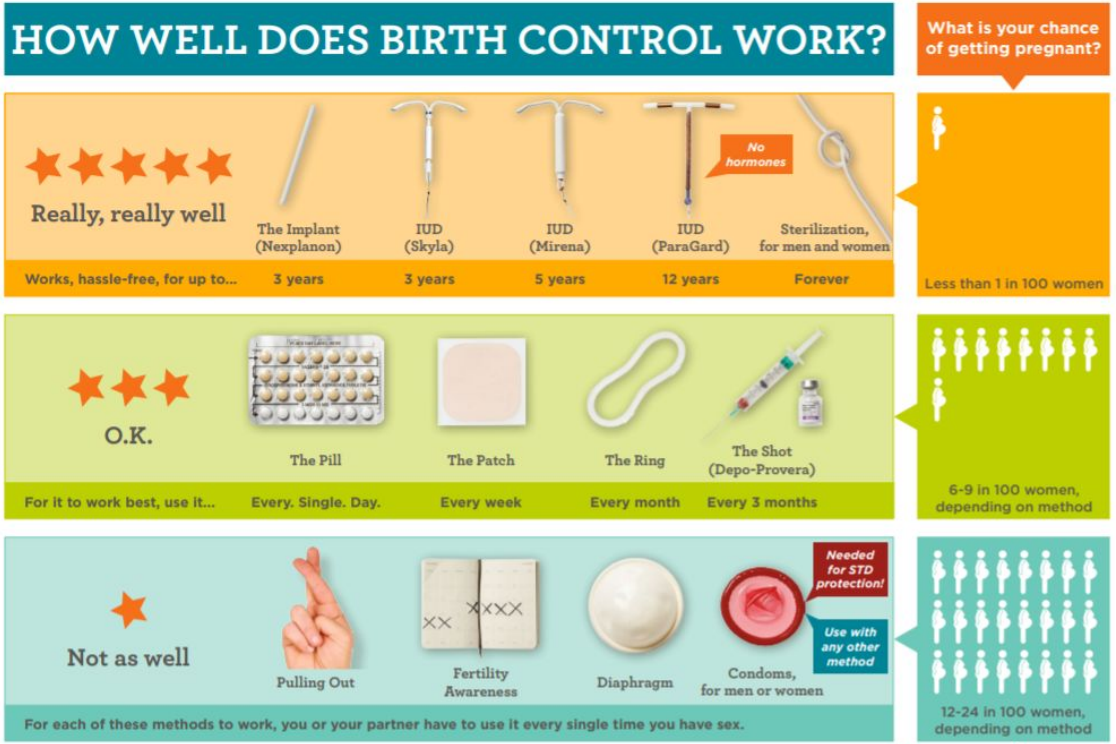
1 in 10 women have unmet need for contraception

Unmet need for contraception

- Sexually active women want to avoid pregnancy but are not using contraception.
- ~ 225 million women in developing regions had an unmet need for modern contraception (2014)
- ~ 74 million unintended pregnancies per year occur in developing regions.
- 52 million unintended pregnancies could be averted by modern contraception.
- 70,000 deaths of women from pregnancy-related causes can be prevented.

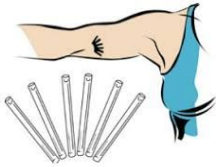
Birth control methods

- Long-Acting Reversible Contraceptives are by far the most effective birth control method



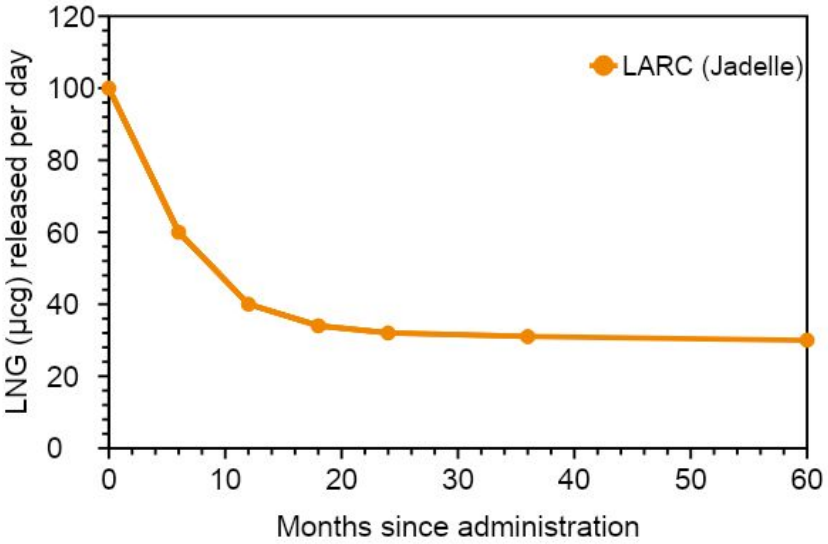
Long-acting reversible contraceptives (LARC)

- Limited access to health clinics and stock-outs increase demand for implants
- Currently used LARC implants require use of trocar (10 G), local anesthesia and aseptic procedures for insertion
- Removal procedure is problematic in resource-constrained settings and requires trained personnel

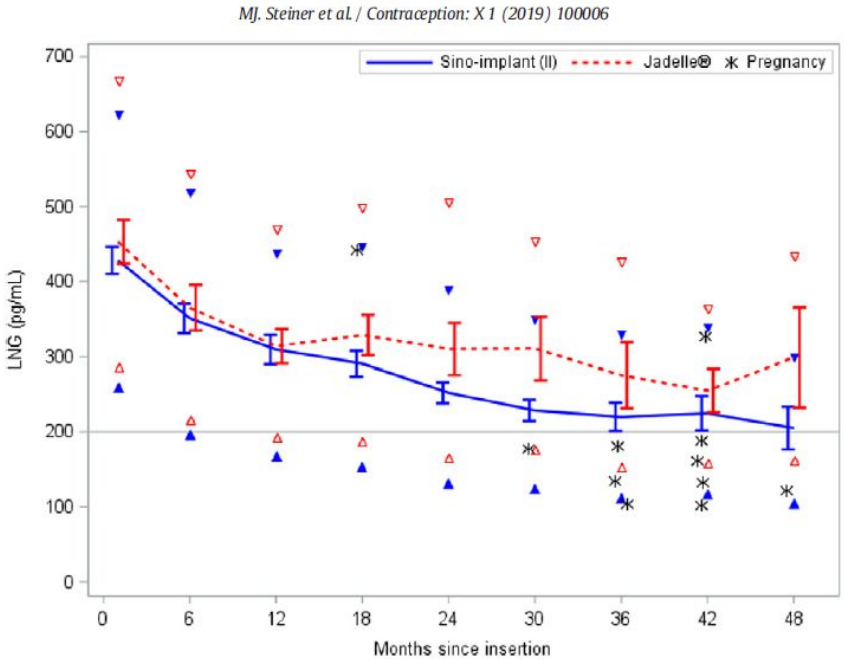


Product	Norplant®	Jadelle®	Implanon NXT®	Levoplant (Sino-implant)
Implants	6	2	1	2
Progestin	Levonorgestrel	Levonorgestrel	Etonogestrel	Levonorgestrel
Dose	6 x	2 x 75 mg	68 mg	2 x 75 mg
Length	34	43 mm	40 mm	43 mm
Diameter	2.4 mm	2.5 mm	2.0 mm	2.5 mm
Polymer	Silicone	Silicone	EVA	Silicone
Duration	5 years	5 years	3 years	3 years

Jadelle and Levoplant (Sino-implant (II))



http://resources.bayer.com.au/



Steiner et al., Contraception 2019
https://doi.org/10.1016/j.conx.2019.100006

Requirements for next generation contraceptive implants for Lower and Middle Income Countries (LMIC)

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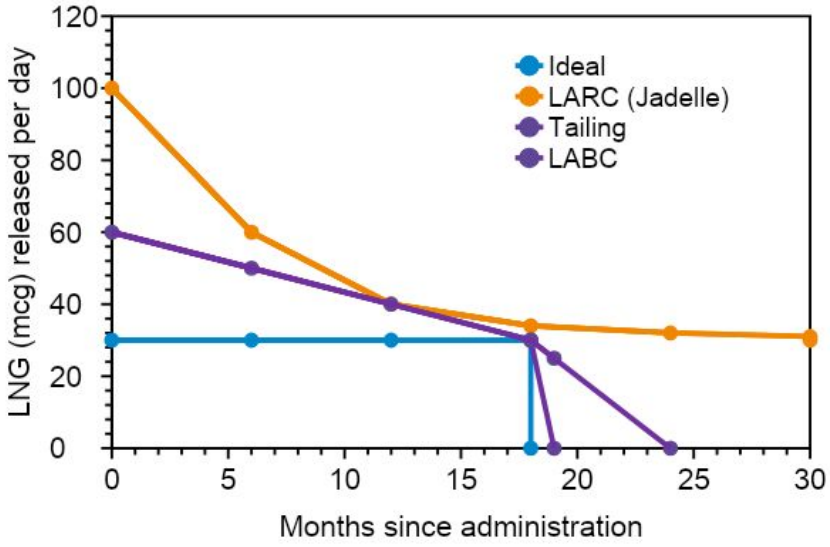
- Bioresorbable to avoid need for removal surgery: **LABC**
- Injectable via small diameter needle (no need for surgical insertion procedure and anesthesia)
- Sustained release at a daily rate of ≥ 30 µg/day to assure constant hormone plasma levels ≥ 200 pg/mL for up to 18 months
- Fast drop of plasma hormone levels at end of therapy to allow rapid return to fertility (RTF)
- Flexible to avoid tissue irritation and extrusion
- Retrievable to allow “immediate” RTF
- Stable under zone IVb storage conditions
- Affordable

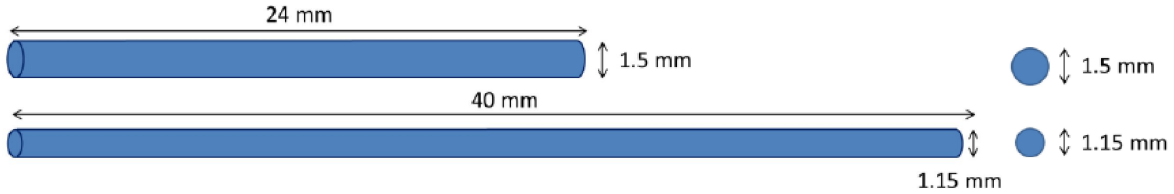
BILL & MELINDA GATES foundation



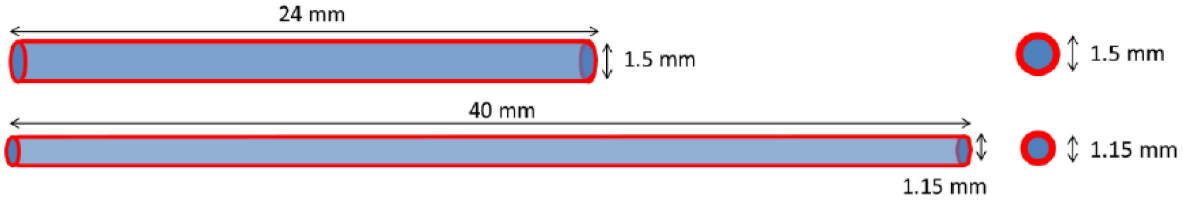
LABC implant design: monolithic matrix vs reservoir system

- **Levonorgestrel (LNG)**
  - 30-60 µg/day
  - 18 months sustained release
  - Dose: 16 – 32 mg
- **One implant**
  - Ø 1.15 - 1.5 mm
  - L 24 - 40 mm
- **LNG loading**
  - 40-50 wt.%
- **14 - 16 G needle injection device**
- **Designs**
  1. Monolithic matrix
  2. Reservoir system with release controlling layer (RCL)
- **Biodegradable polymer(s)**
- **Hot melt extrusion (HME)**

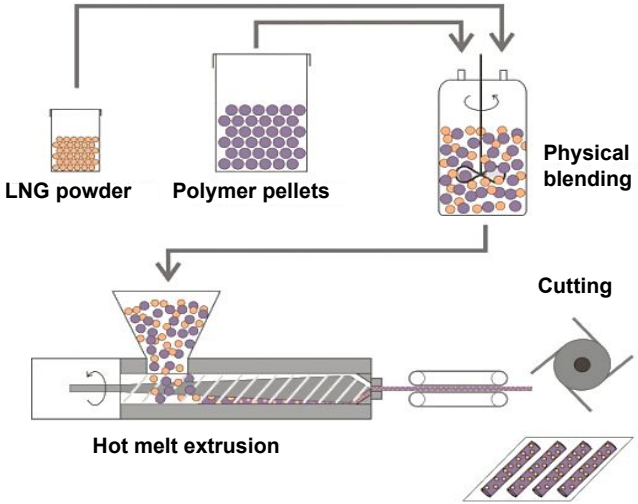
- **Monolithic matrix**

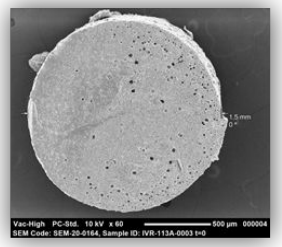


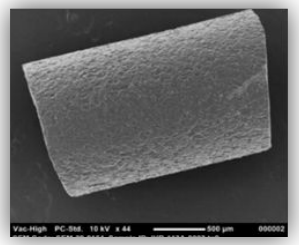
- **Reservoir system with release controling layer (RCL)**

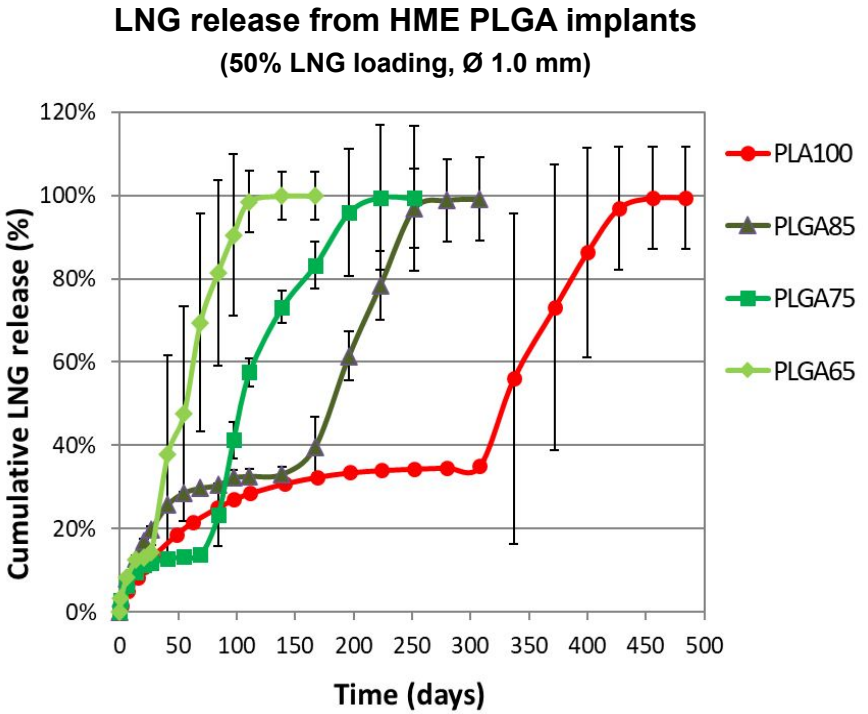


HME monolithic LNG implants – PLGA Formulation development

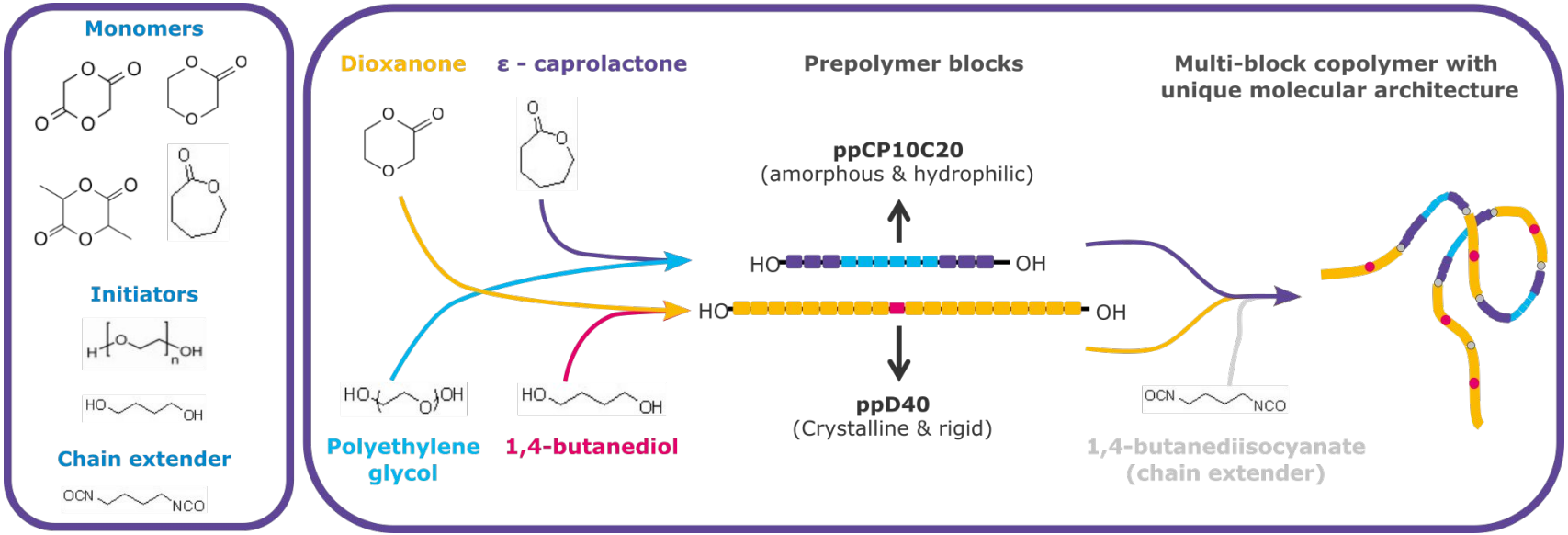




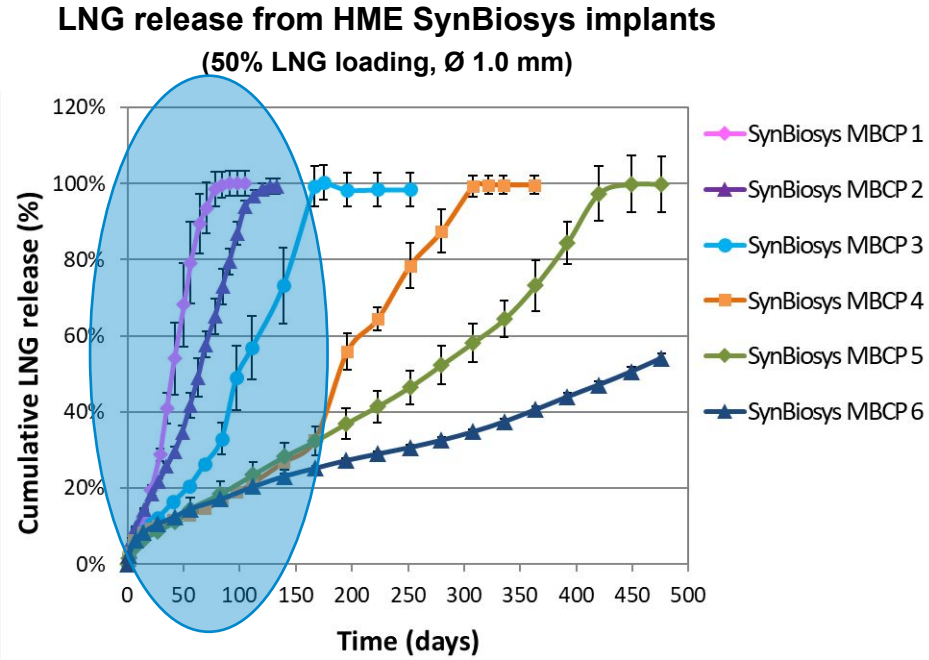




Bioresorbable polyether ester urethane copolymers (SynBiosys®)



HME monolithic LNG implants – SynBiosys multi-block copolymers
Formulation development



Characteristics

- Linear release of LNG
- Release duration controlled by polymer composition

Establish in vitro in vivo correlation (VIVC)

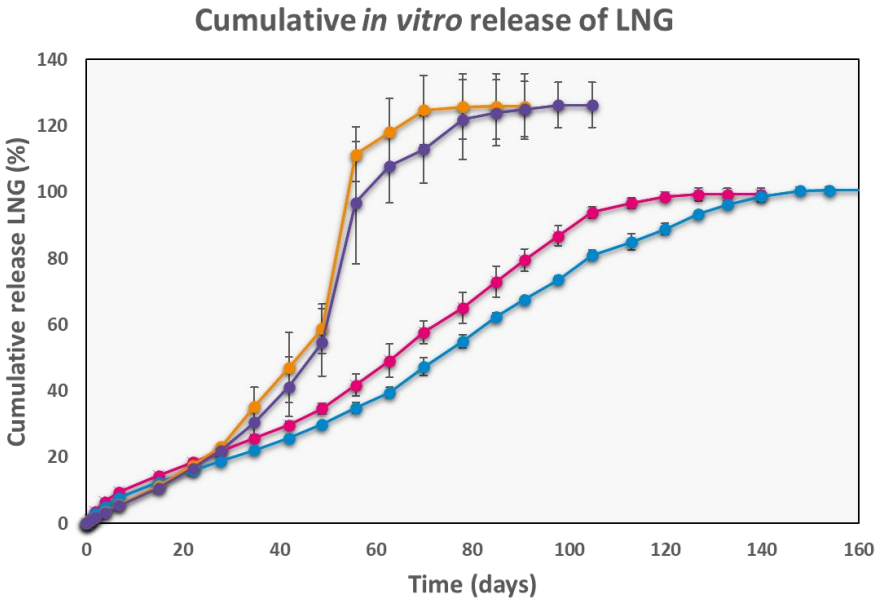
- Short term releasing implants

SynBiosys polymer platform was selected as it provides more constant release of levonorgestrel thereby preventing large fluctuations in plasma levels

HME monolithic LNG implants – SynBiosys
Model LNG implant formulations for *IVIVC* assessment

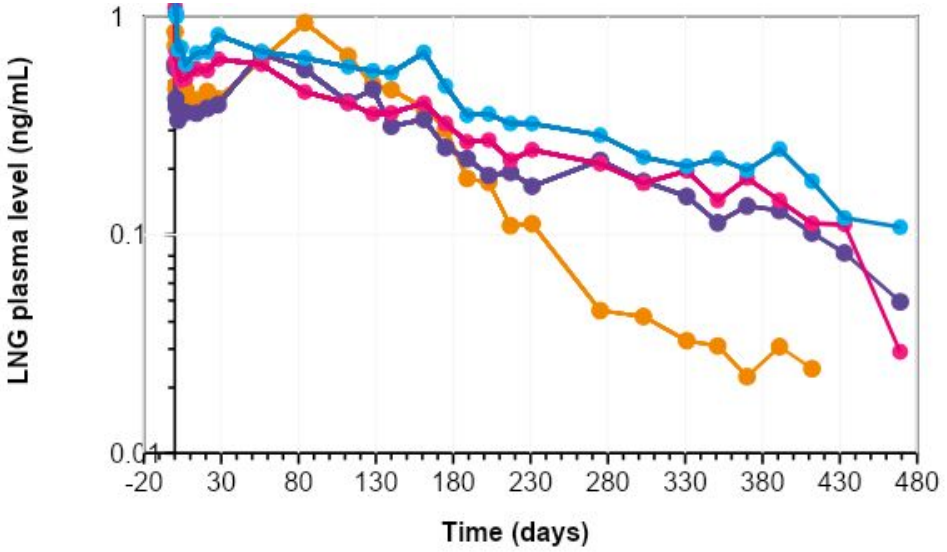
- **Test IVIVC for different LNG implant formulations**
  - Polymer composition (= polymer degradation kinetics)
  - Implant diameter
  - Implant length
  - LNG dose
  - In vitro release kinetics

Formulation	Polymer	Ø x L (mm)	LNG (mg)
1A	MBCP 1	1.10 x 9	4.2
1B	MBCP 1	1.45 x 5	4.6
2A	MBCP 2	1.10 x 9	4.7
2B	MBCP 2	1.45 x 10	9.3



HME monolithic LNG implants – SynBiosys
In vivo pharmacokinetics

- Female Sprague-Dawley rats
  - 4 rats per group
- Anticipated release duration 3-4 months (based on in vitro release)
- Anticipated release 30 µg LNG / day corresponding with
  - 200 pg/mL in women
  - 1 ng/mL in rats
- Based on significantly lower plasma levels in life study duration extended to 6+ months
- *In vivo* release significantly slower than *in vitro*
- Polymer 2 allows constant release of LNG with gradually decreasing plasma levels up to ≥ 15 months



Formulation	Polymer	Ø x L (mm)	LNG (mg)
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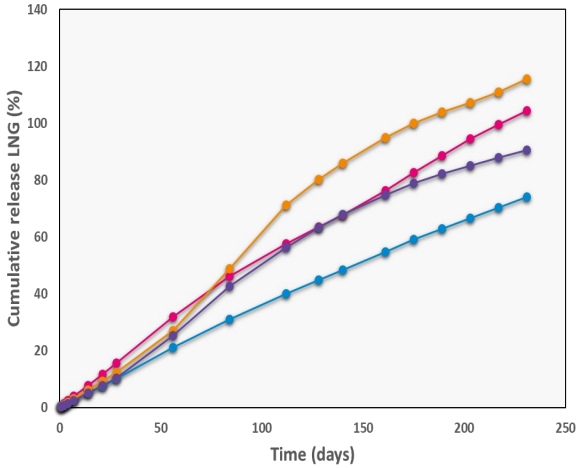
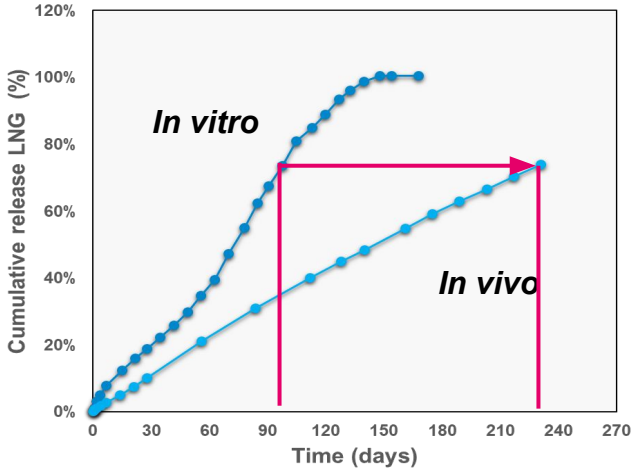
1B	MBCP 1	1.45 x 5	4.6
2A	MBCP 2	1.10 x 9	4.7
2B	MBCP 2	1.45 x 10	9.3

HME monolithic LNG implants – SynBiosys
In vivo – In Vitro Correlation (IVIVC)

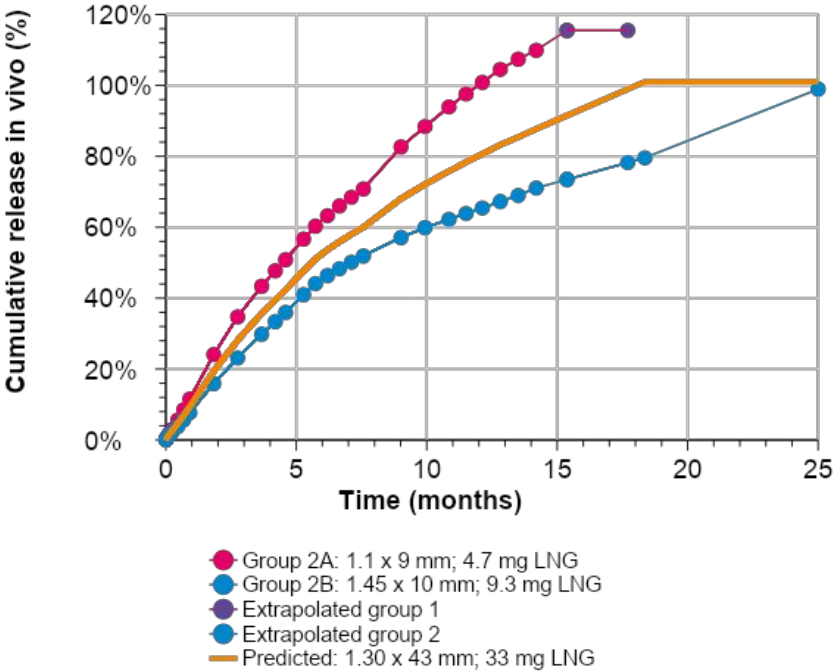
- ***In vivo*** **pharmacokinetics of Levonorgestrel were analyzed using PK Solver, v 2.0 (Non-compartmental modeling)**
- ***In vivo*** **release is significantly slower compared to *in vitro* release (2 – 3 times)**
- **Release rate decreases with implant diameter**

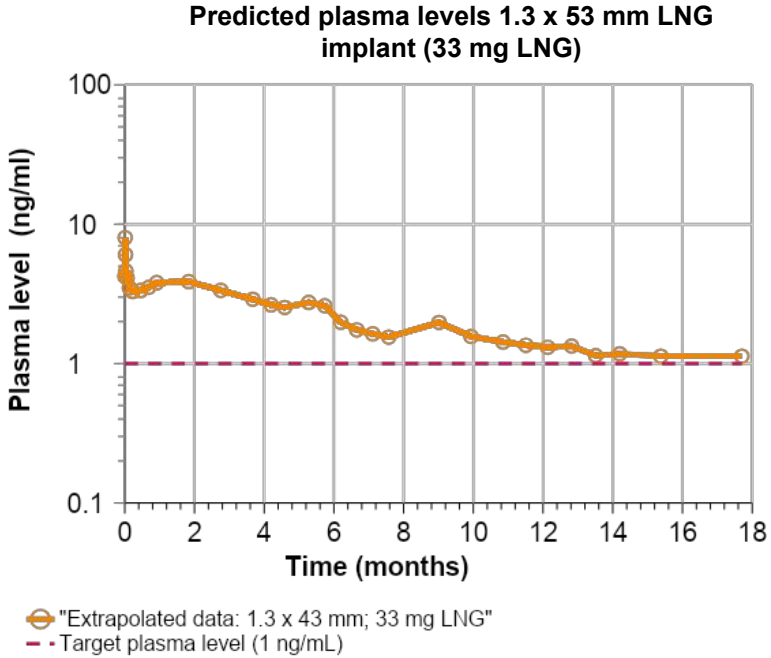




Formulation	Polymer	Ø x L (mm)	LNG (mg)	t1/2 (days)	AUC (0-t) (ng/mL*day)	F (%)
1A	MBCP 1	1.10 x 9	4.2	84	115	115
1B	MBCP 1	1.45 x 5	4.6	85	90	91
2A	MBCP 2	1.10 x 9	4.7	154	104	104
2B	MBCP 2	1.45 x 10	9.3	361	148	74

HME monolithic LNG implants – SynBiosys
Design of 18 months LNG implant





1.3 x 43 mm implant with a dose of 33 mg LNG expected to be suitable as a 18 months LABC

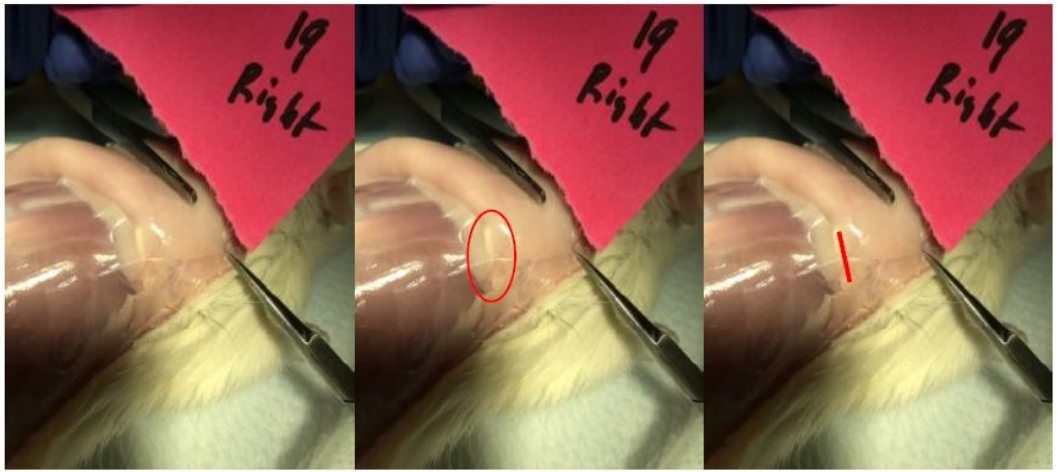
Implant retrievability
Monolithic LNG implants

- **Retrievability assessed qualitatively during *in vivo* PK study**
  - **t = 10, 28, 56 days**
  - **t = 202 days post mortem**

- **Implants are intact up to 6 months**

Study 1054-002, Implant Retrieval

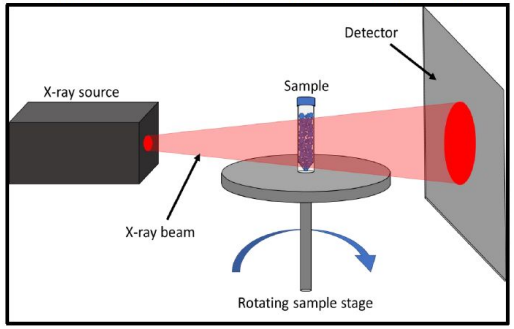
Group 7, Rat no. 19, Day 56



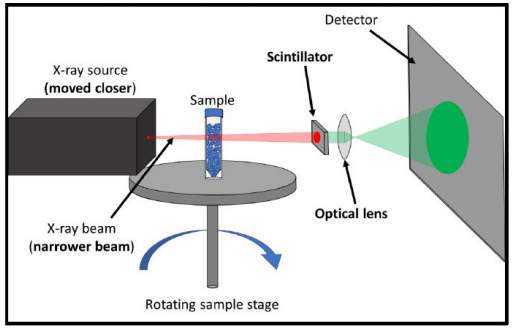
X-ray microscopy (XRM) and modelling for better understanding and prediction of of release kinetics

- **Visualize Internal Microstructures**
  - 3D imaging techniques by X-ray microscopy (XRM) to visualize internal structures of long-acting drug products.
  - investigation of microporosity, drug particles, and polymer.
- **Predict Release Performance**
  - Patented algorithms to simulate drug release and transport properties directly from 3D imaging data
  - Correlation and optimization of drug performance through microstructures.
    - Permeability
    - Tortuosity
    - Effective diffusivity
    - Mercury injection capillary pressure (MICP) porosimetry
    - Image-based release prediction

MicroCT (resolutions as high as 10 µm/voxel)



XRM (resolutions as high as 500 nm/voxel)

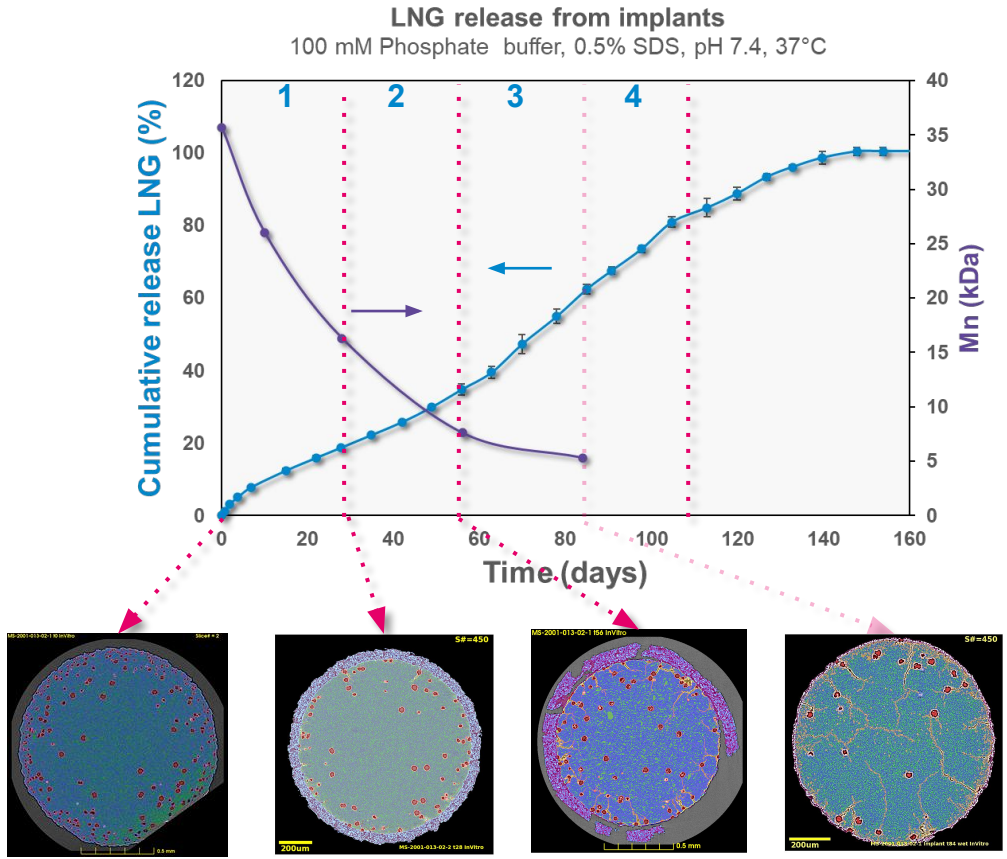


❖ XRM not only allows for high resolution viewing of a region of the sample, but it also avoids common artefacts of computed tomography/MicroCT including beam hardening due to the sample container, allowing for both high resolution as well as excellent contrast.

Imaging: Experimental design - sample preparation
Analysis: Proprietary machine learning and deep learning technologies
Simulation: Cloud computing infrastructure and data management

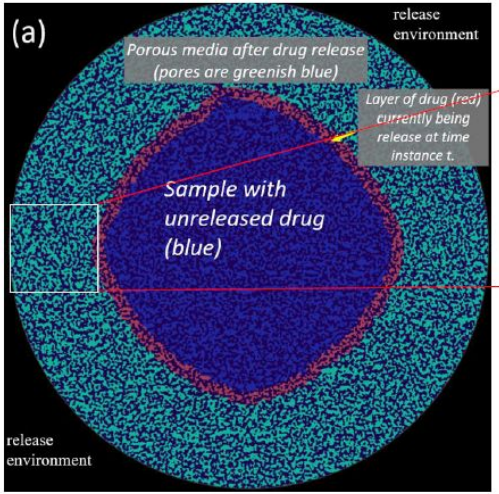
Mechanism of LNG release

1. **Monolithic release**
   - Diffusion driven (through pre-existing LNG network)
2. **Monolithic release with initial erosion influence**
   - Highly porous outer ring is formed
   - Fractures formed inside inner core
   - Constant release rate obtained
3. **Degradation (fracture) driven release**
   - Detachment of porous ring from implant
   - Accelerated crack formation increases the release rate
4. **Monolithic release through cracks**
   - Reduced fracture growth and influence of erosion
   - Release is governed by diffusion of LNG through preformed cracks

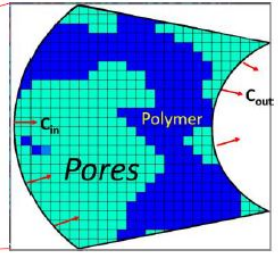


XRM-based modelling to predict *in vitro* release

1. Percolation Simulation → 2. Effective Diffusivity → 3. Physical Time Conversion



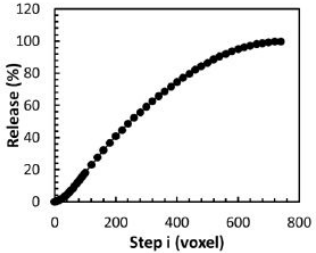
Determines the drug release as a function of time using only the sample microstructure



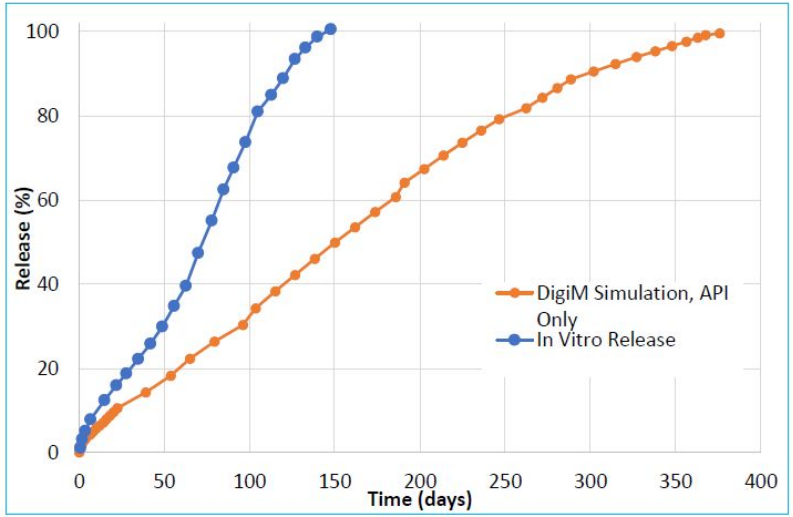
Solves Fick's Law to obtain the time dependent diffusion coefficient

A known release model is used to obtain a physical time conversion of the released drug (Zero order model, Higuchi model, etc.)

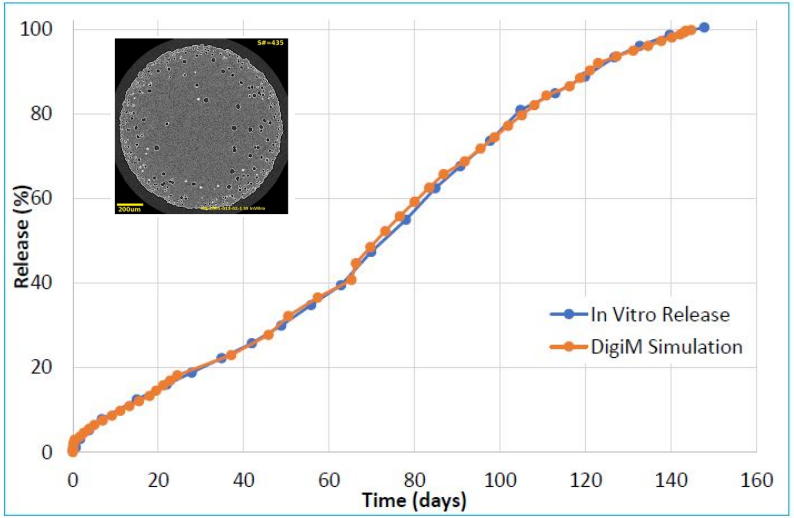
Percolation simulation



XRM-based modelling to predict *in vitro* release HME monolithic LNG implants – SynBiosys



Release prediction taking into account ONLY API network at t = 0 days



Release prediction taking into account both API and pore network at t = 0 days

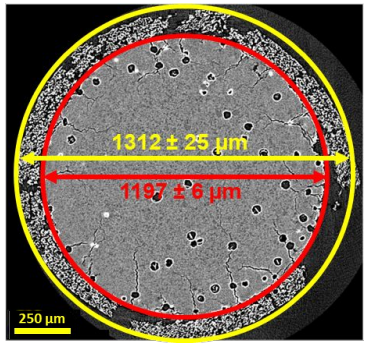
In vitro vs *in vivo* degradation and morphological differences

- ***In vitro***
  - Delamination porous outer layer
  - Crack formation
  - outer implant diameter similar to full diameter of implant *in vivo*
- ***In vivo***
  - no delamination layer
  - No crack formation
  - severally eroded implant at 240 days and outer layer with little to no porosity and a highly porous inner region
- **Degradation follows different trend *in vitro* vs. *in vivo***

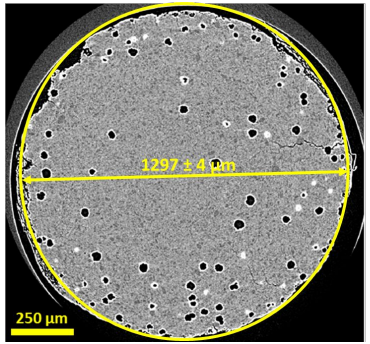
T = 56 days

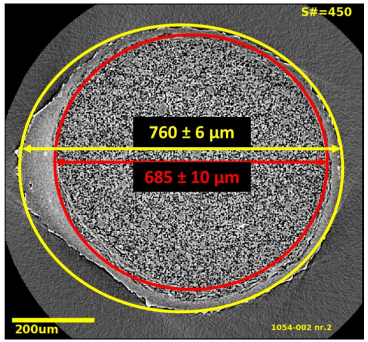
T = 240 days

In vitro

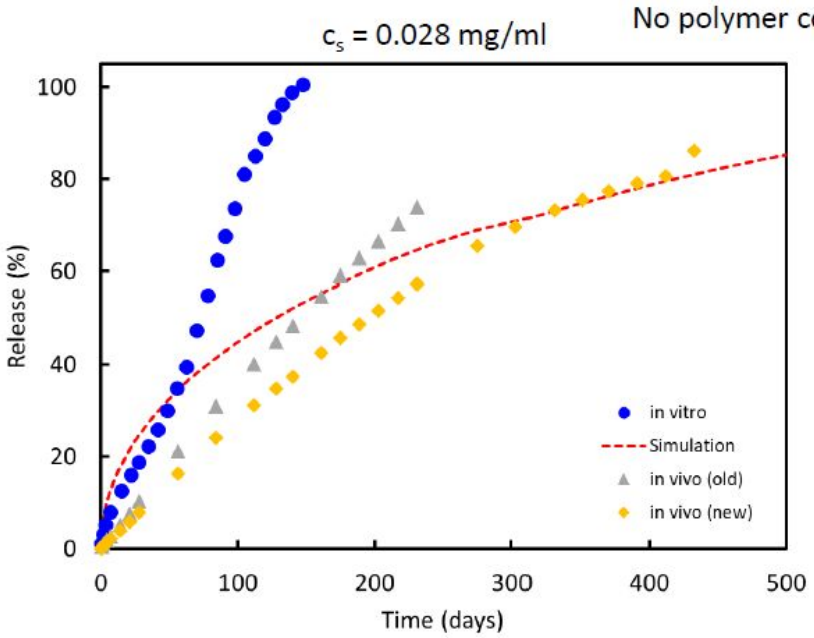


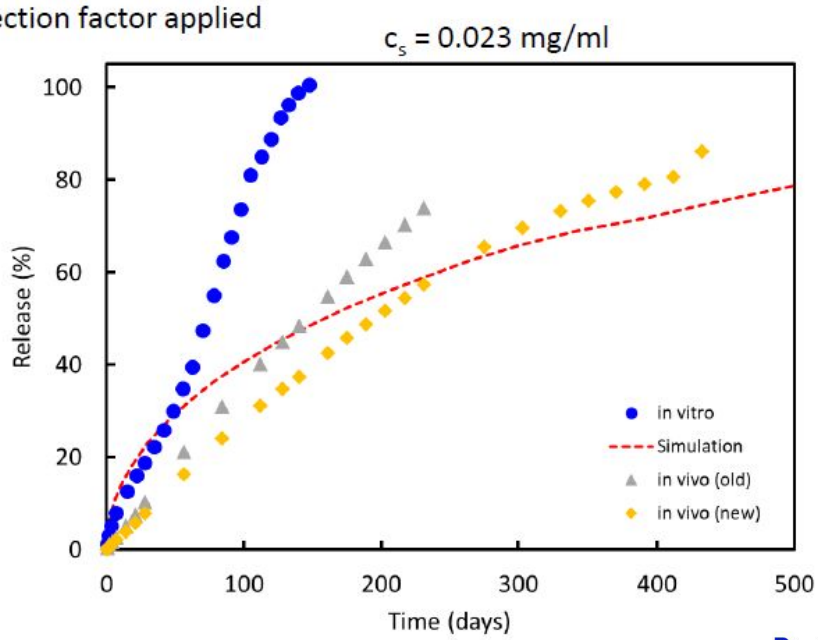
In vivo



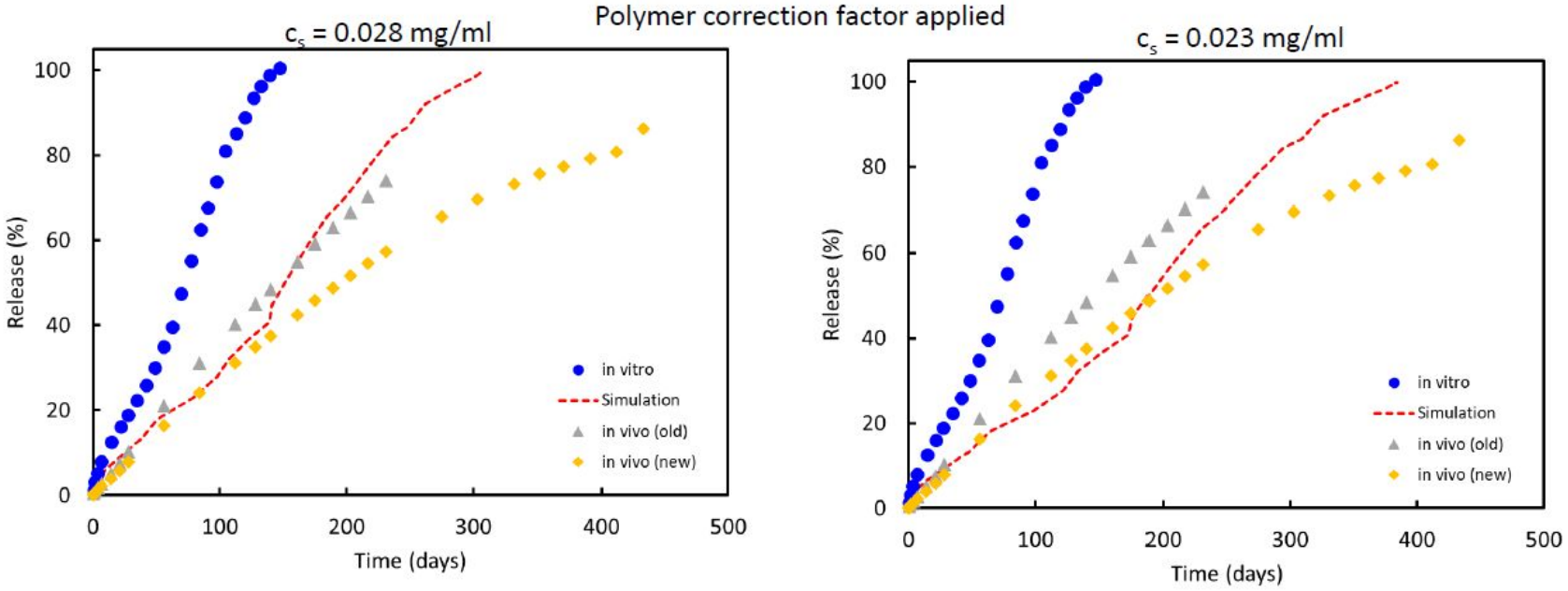


Simulation of *in vivo* release
HME monolithic LNG implants – SynBiosys



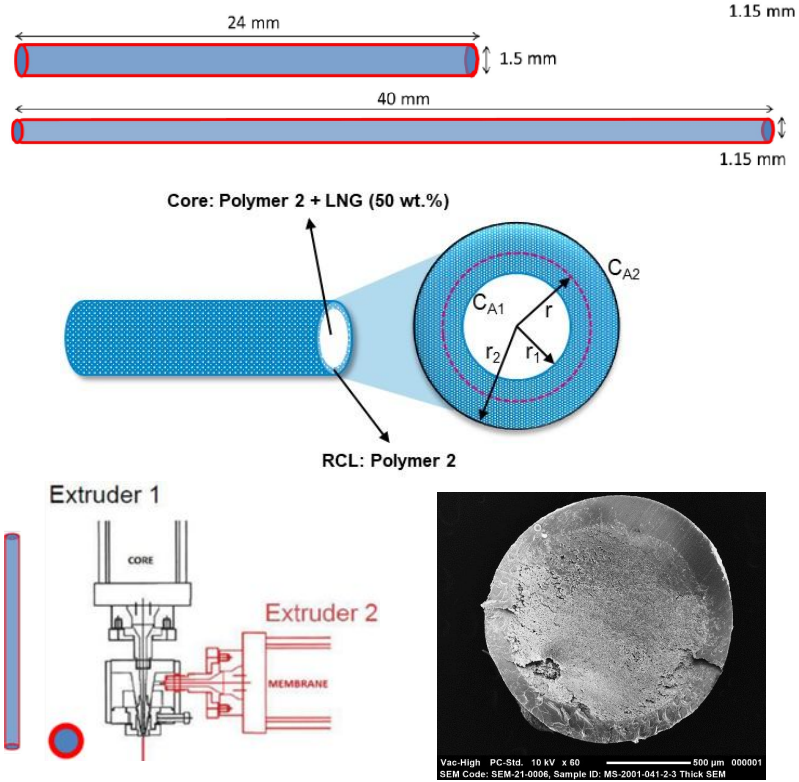


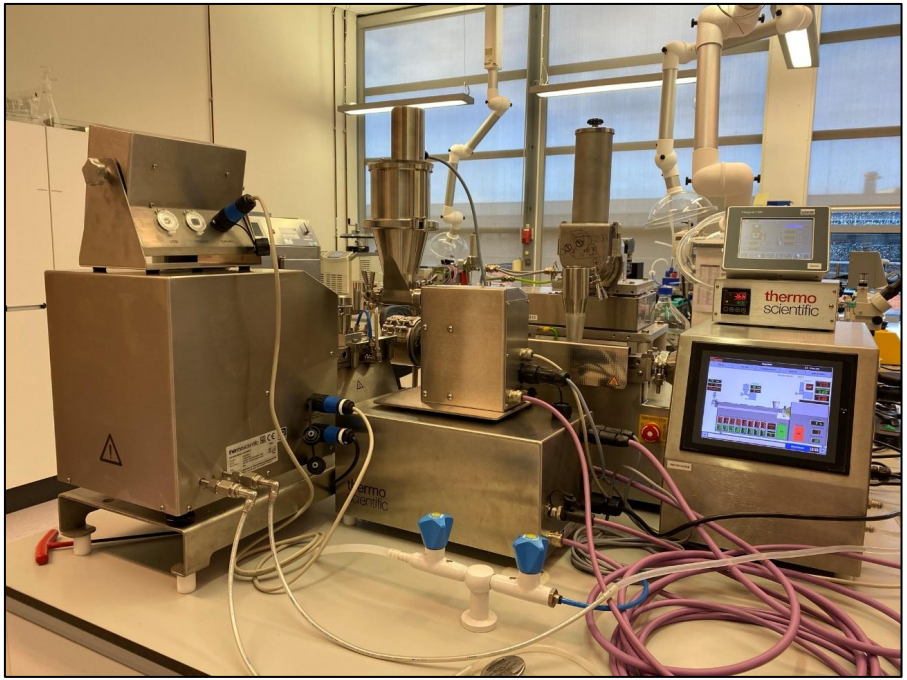
Simulation of *in vivo* release
HME monolithic LNG implants – SynBiosys



Release simulation captures *in vivo* release well up to ~275 days

Reservoir-type LNG implants with release controlling outer layer





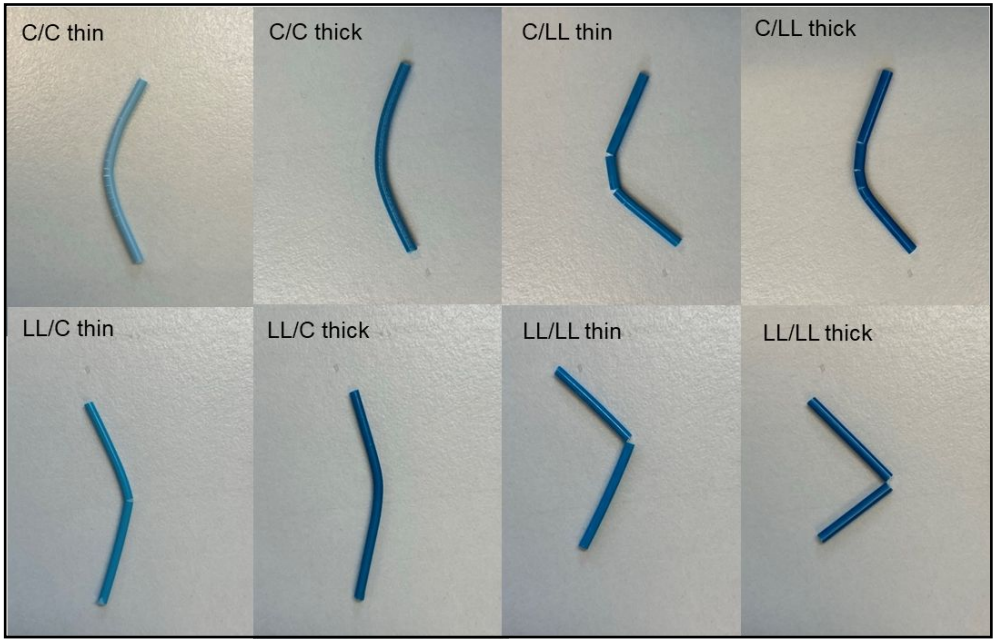
HME reservoir-type LNG implant with RCL
Design of Experiments (1)

- **Formulation variables**
  - Core polymer grade
  - Core diameter
  - Coating polymer grade
  - Coating thickness
  - (LNG loading)
  - Implant diameter

- **Output**
  - Manufacturibility
  - Mechanical characteristics
  - Release kinetics

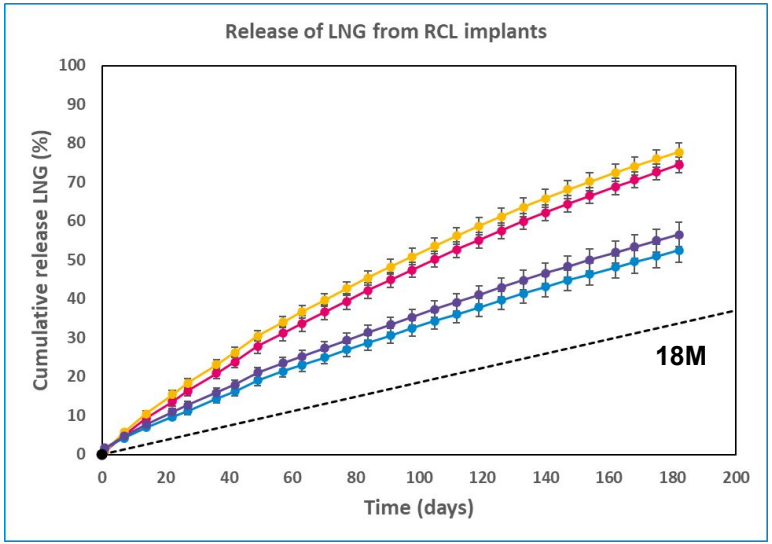
Formulation	Core			RCL		Complete implant	
	Polymer	Diameter (mm)	LNG loading (%)	Polymer	Thickness (µm)	LNG loading (%)	Diameter (mm)
1	MBCP-01	0.82-0.92	51.7	MBCP-01	140-190	28.7	1.2
2	MBCP-01	1.02-1.11	51.7	MBCP-01	45-95	39.9	1.2
3	MBCP-01	1.16-1.28	51.7	MBCP-03	160-220	28.8	1.6
4	MBCP-01	1.20-1.35	51.7	MBCP-03	74-150	39.6	1.5
5	MBCP-02	1.11-1.14	51.2	MBCP-01	80-95	38.8	1.3
6	MBCP-02	1.19-1.20	51.2	MBCP-01	50-55	43.6	1.3
7	MBCP-02	1.22-1.28	51.2	MBCP-03	110-140	33.7	1.5
8	MBCP-02	1.29-1.34	51.2	MBCP-03	30-55	45.1	1.4

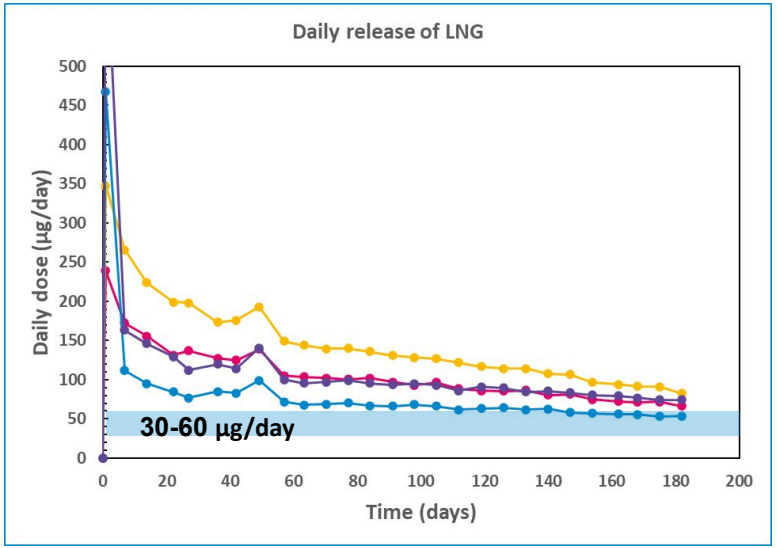
Reservoir-type LNG implants with RCL
Mechanical characteristics



Test for quantitative mechanical testing under development

HME reservoir-type LNG implant with RCL
In vitro release kinetics

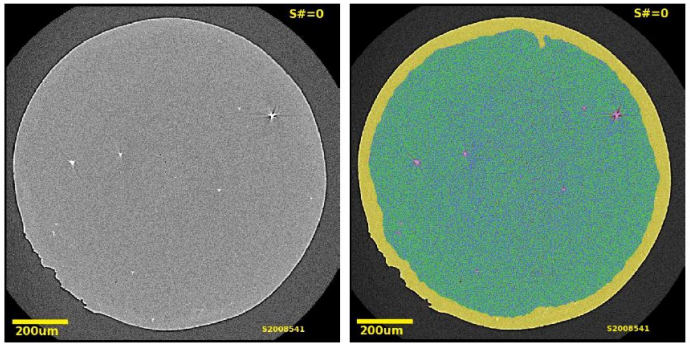




Sample	Polymer I (Core)	Polymer II (Shell)	Dose (mg)	LNG loading (%)
●	MBCP-1	MBCP-05	25	39.0
●	MBCP-1	MBCP-05	33	39.0
●	MBCP-4	MBCP-06	25	41.4
●	MBCP-4	MBCP-06	33	41.4

Close to linear release observed for all RCL LNG implant formulations

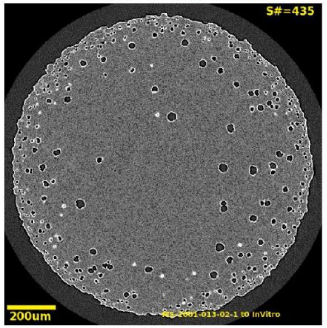
XRM 3D-imaging of reservoir-type LNG implant with RCL



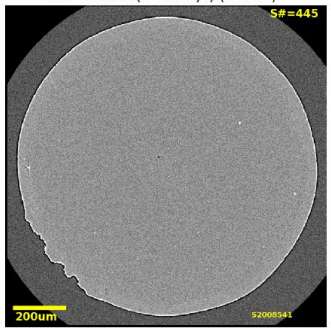
Pores; API; Polymer; Hi-Density; Out-Layer

Overview	D3334
Resolution (µm)	1.6
Dimensions (pixels)	831 x 831 x 885
Dimensions (µm^3)	1289 x 1289 x 1372
Total Diameter (µm)	**1207 ± 1**
Sheath thickness (µm)	**50 ± 8**
Pores (%)	**1.4**
Polymer(%)	**54.7**
API (%)	**43.7**

Monolithic (t = 0 days) (D1320)



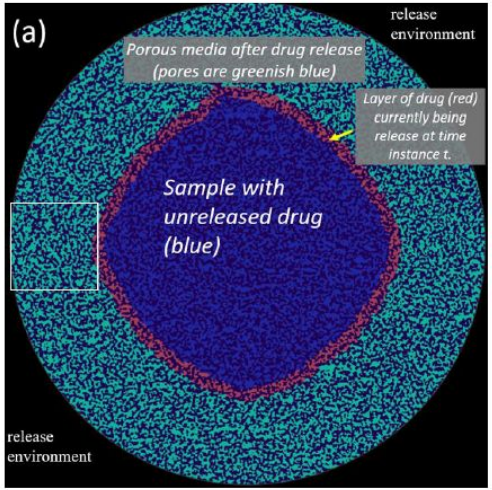
Core-sheath (t = 0 days) (D3334)



Little to no porosity in LNG implants with RCL
Significant porosity in monolithic implants

XRM-based modelling to predict *in vitro* release: *Reservoir-type LNG implant with RCL*

1. Percolation Simulation → ~~2. Effective Diffusivity~~ → 3. Physical Time Conversion



Determines the drug release as a function of time using only the sample microstructure

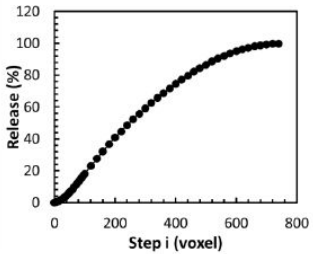
Membrane systems control the rate of diffusion out of the implant.

Diffusion across the membrane is far slower than the rate of diffusion of the API within the core to the inner edge of the membrane.

This means that only the bulk diffusion across the membrane is needed for physical time conversion.

A known release model is used to obtain a physical time conversion of the released drug (Zero order model, Higuchi model, etc.)

Percolation simulation

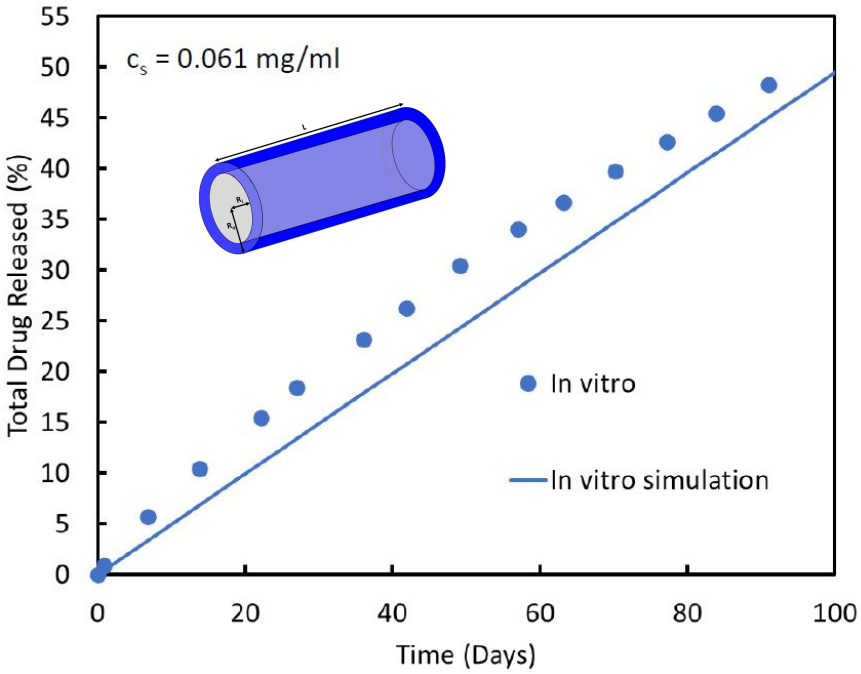


XRM-based modelling to predict *in vitro* release
Reservoir-type LNG implant with RCL

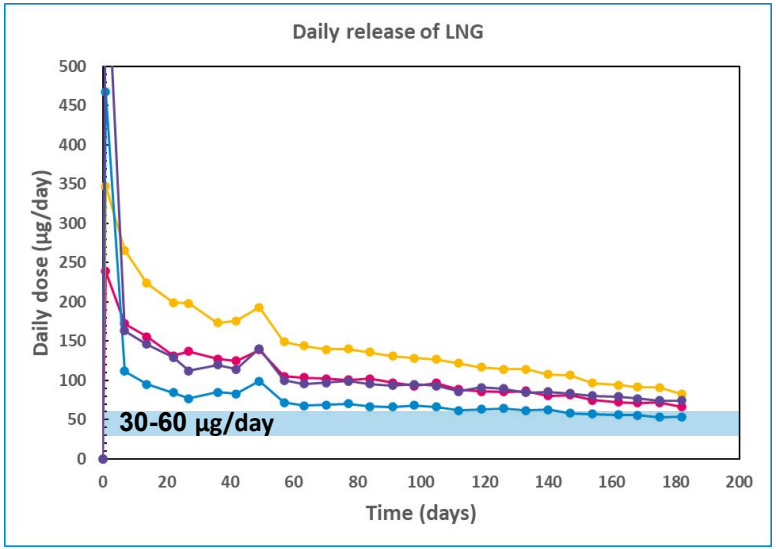
$$t = \frac{\ln\left(\frac{r_2}{r_1}\right) M_t}{2\pi K L D_{AB}(c_{A1} - c_{A2})}$$

Release Parameter	Value
R_o Outer radius (µm)	603.5
R_i Inner radius (µm)	578.5
M_t (mg)	**Simulated parameter**
L Implant length (cm)	0.1371*
D_{eff} Effective diffusivity (cm^2/s)	$6x10^{-6}$
c_s Drug solubility (mg/cm^3)	0.061**
K Partition coefficient	1***

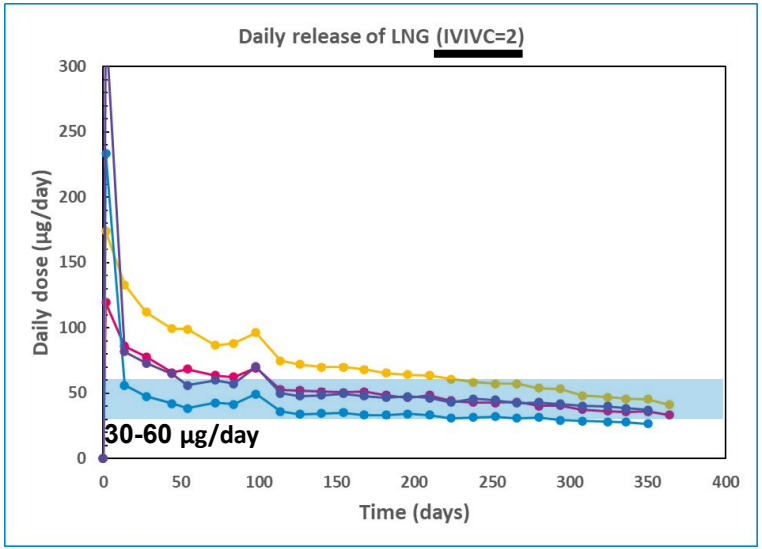
**Length determined from imaging volume*
***In vitro solubility reported here*
****Temporary value until experimentally measured value is determined*



HME reservoir-type LNG implant with RCL
In vitro release kinetics and anticipated *in vivo* release duration



IVIVC ?



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RCL implants with different polymer structure are expected to release for the desired duration (18-24 months) in case of similar IVIVC as monolithic implants

Concluding remarks

- **Long-acting bioresorbable implants offer long-term and well-controlled sustained release of levonorgestrel**
  - Monolithic matrix or reservoir-type implants with release controlling layer
  - *In vivo* erosion and release kinetics significantly different from *in vitro*
- **X-ray microscospy provides a strong supporting development tool for LABC implants**
  - Mechanistic understanding of release mechanism
  - Predictive modelling of release kinetics
- **Long-term *in vivo* PK and retrievability studies**
  - *In vivo* PK
  - IVIVC (especially reservoir-type implants with RCL)
  - feasibility of 18 month releasing LNG implants
  - Tailing
  - Retrievability

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innocore PHARMACEUTICALS

Ivan Terzic
Mark Staal
Albert Doornbos
Inge Kok
Arjen Funhoff
Thanh Nguyen

www.innocorepharma.com
T: +31-505753100 - E: info@innocorepharma.com

innocore PHARMACEUTICALS

Thank you!

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T: +31-505753100 - E: info@innocorepharma.com

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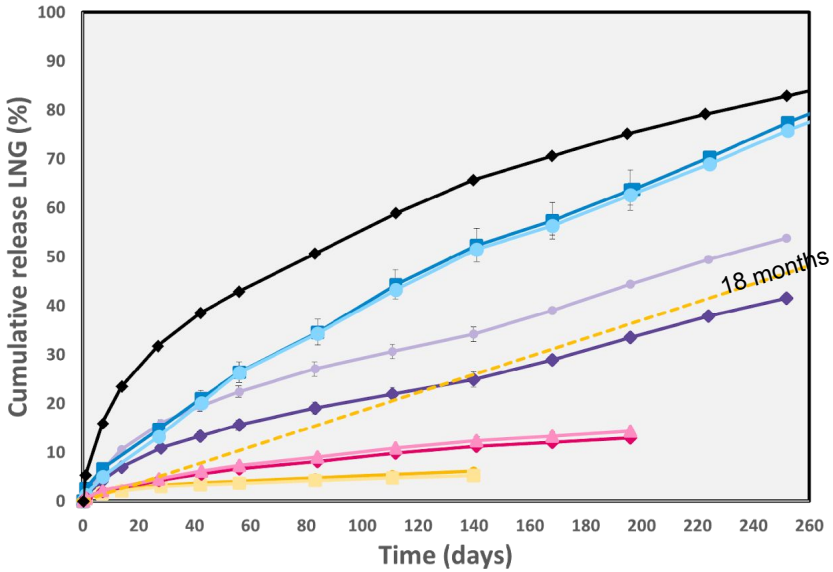
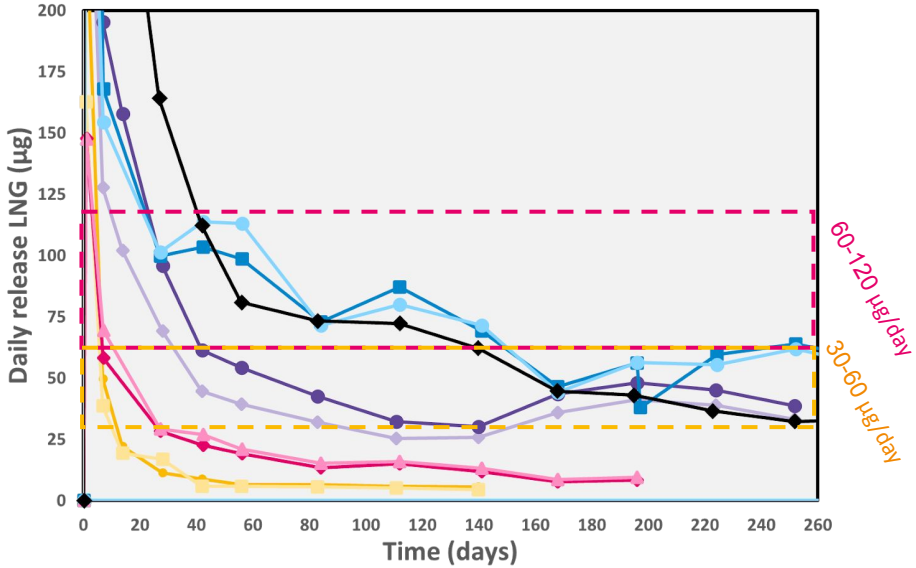
- RCL concept reduces initial burst
- Close to linear release can be obtained
- Type of polymer in both core and RCL impacts the release rate
- Thickness of RCL has less or no effect on release rate in the tested range

HME reservoir-type LNG implant with RCL
In vitro release kinetics





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- Close to linear release can be obtained
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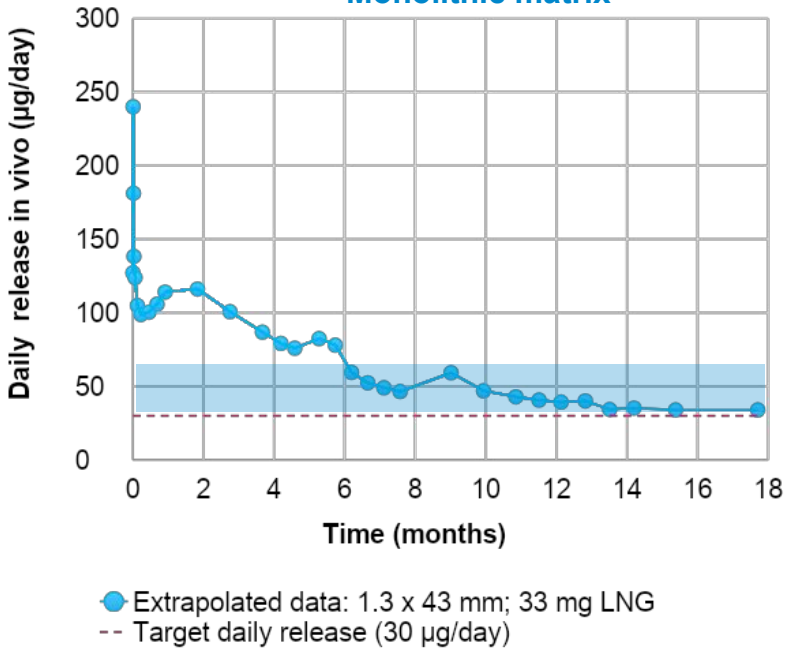
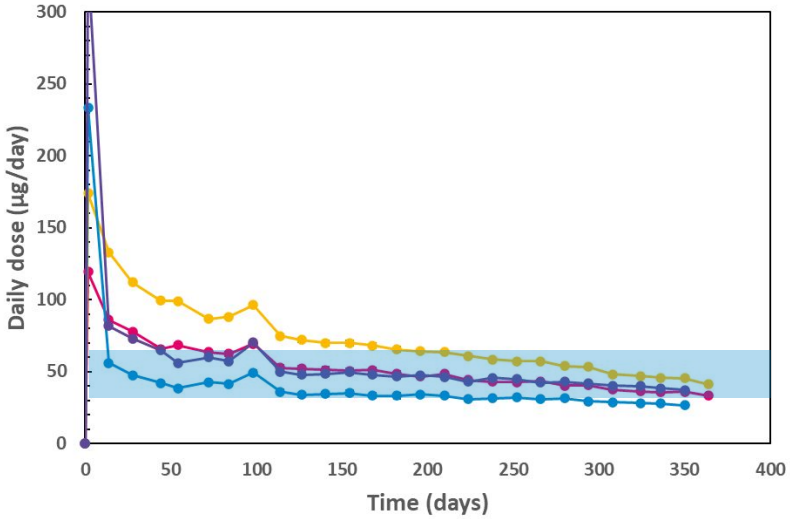
Can we expect similar *in vivo* LNG release kinetics expected for monolithic implants and reservoir-type implants with RCL

Monolithic matrix



Reservoir-type implant with RCL



Next

- **Further optimization of the drug release model**
  - **Optimize release model to predict in vivo release**
- **Long-term in vivo PK studies**
  - **Optimized monolithic implants**
  - **Alternative animal model**
    - Rats survival rate 31 % at 15 months
  - **IVIVC reservoir-type implants with RCL**
  - **End-of-treatment tailing**
  - **Retrievability**
- **Erosion kinetics**
  - **In vitro and in vivo; IVIVC**
- **Process optimization**
- **Sterilization studies**
- **Storage stability**