LAPaL
THE LONG-ACTING THERAPEUTICS PATENTS AND LICENCES DATABASE

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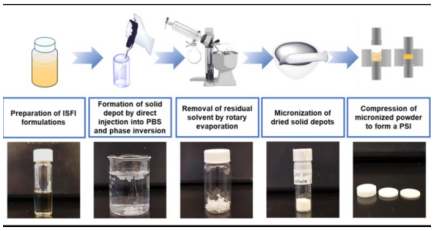


# Tunable Biodegradable Ultra-Long-Acting Polymeric Solid Implant (PSI)

Verified by the innovator, on Apr 2022

## Developer(s)

University of North Carolina at Chapel Hill
https://benhabbour.web.unc.edu/

United States

Our research at the Benhabbour Lab focuses on engineering novel tunable delivery platforms and polymer-based devices that can treat or prevent a disease. Our work combines the elegance of polymer chemistry with the versatility of engineering and formulation development to design and fabricate efficient and translatable delivery systems for a wide range of applications.

## Sponsor(s)


NIH-NIAID

https://www.niaid.nih.gov/

UNC CFAR

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# Partnerships

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# Technology information

## Type of technology

Polymeric implant

## Administration route

Subcutaneous

## Development state and regulatory approval

**Active Pharmaceutical Ingredient (API)**

Dolutegravir (DTG)

**Development Stage**

Pre-clinical

**Regulatory Approval**

None

## Description

Ultra-long-acting (ULA) biodegradable polymeric solid implant (PSI) that can accommodate one or more APIs (e.g. ARVs) at translatable human doses in a single implant, in a form of single or multi-layer multi-drug PSI. Administered subcutaneously, PSIs are well tolerated in vivo and effectively delivered drug(s) over 180 days, achieving plasma concentrations above therapeutic targets. While biodegradable, these PSIs can safely be removed to terminate the treatment if required. The versatility of this technology makes it attractive as an ULA drug delivery platform for HIV and other applications.

## Technology highlight

Biodegradable polymeric solid implants (PSIs) are fabricated using phase inversion of drug-loaded polymer-based solution in combination with a compression technique that allows fabrication of PSIs with high drug loading (up to 85 wt%) and compact sizes. The fabrication of these PSIs is accomplished using a simple and scalable stepwise process of (1) phase inversion of a drug-loaded polymer-based solution to form an initial in-situ forming solid implant in an aqueous medium, (2) micronization of dried drug-loaded solid implants, and (3) compression of micronized drug-loaded solid powder. The resulting PSIs are solvent-free and consist of only the biodegradable polymer and drug(s). The manufacturing process does not require high heat or high pressure and can be easily scalable.

## Technology main components

Poly(DL-lactide-co-glycolide (PLGA) or other biodegradable polymers (e.g. PLA, PCL)

### Information on the raw materials sourcing, availability and anticipated price

Raw materials are readily available on the market

## Delivery device(s)

No delivery device

# APIs compatibility profile

## API desired features

### Water-soluble molecules

### Water-insoluble molecules

### Small molecules

Dolutegravir, Rilpivirine, Cabotegravir

### Nucleic acids

Confidential

### Proteins

Confidential

### Additional solubility data

Not provided

### Additional stability data

Not provided

### API loading: Maximum drug quantity to be loaded

75-90 wt%

## API co-administration

2 different APIs : at least 2

## LogP

Not provided

# Scale-up and manufacturing prospects

## Scale-up prospects

Scalability anticipated. Additional information needed.

## Tentative equipment list for manufacturing

Additional information needed

## Manufacturing

New fabrication process using phase inversion and compression. Does not use high heat, high pressure or large volumes of organic solvents. Additional information needed.

## Specific analytical instrument required for characterization of formulation

Additional information needed

# Clinical trials

Not provided

# Excipients

## Proprietary excipients used

No proprietary excipient used

## Novel excipients or existing excipients at a concentration above Inactive Ingredients Database (IID) for the specified route of administration

No novel excipient or existing excipient used

## Residual solvents used

Dimethyl Sulfoxide (DMSO)

# Additional features

## Other features of the technology

- Biodegradable
- Drug-eluting
- Monolithic
- Removable
- Single-use
- Room temperature storage
- At least 1 year shelf life

## Release properties

Slow diffusion of the drugs through degradation of the PLGA matrix by hydrolysis of ester linkages in the presence of water, with minimal initial burst.

## Injectability

Additional data needed

## Safety

Well tolerated in vivo (BALB/c mice) over six months. No signs of toxicity, behavioural changes, water consumption, weight loss. Histological staining analysis shows minor inflammation, substantially decreasing 2 weeks after injection. Plasma cytokines showed no systemic acute or chronic inflammation observed.

## Stability

Additional data needed

## Storage conditions and cold-chain related features

Additional data needed

# Potential application(s)

## Therapeutic area(s)

Disease agnostic

HIV

HBV

TB

COVID 19

Contraception

Multipurpose technology : "Prevention of STIs and unplanned pregnancy"

Pain management

Oncology

Diabetes

### Use case(s)

Pre-Exposure Prophylaxis (PrEP)

Treatment

## Use of technology

### Ease of administration

- Administered by a community health worker
- Administered by a nurse
- To be determined

### Frequency of administration

Bi-yearly

## User acceptance

To be determined

## Targeted user groups

### Age Cohort

- Adults

### Genders

- All
- Male
- Female
- Cisgender female
- Cisgender male
- Transgender female
- Transgender male
- Intersex
- Gender non-binary

### Pregnant individuals

Yes

### Lactating individuals

Yes

### Healthy individuals

Unspecified

### Comment

To be further investigated

# Potential associated API(s)

## Dolutegravir (DTG)

### Class(es)

Not provided

### Development stage

Pre-clinical

### Clinical trial number(s)

None

### Foreseen/approved indication(s)

Not provided

### Foreseen user group

Not provided

### Foreseen duration between application(s)

Not provided

### Applications to Stringent Regulatory Authorities (SRA) / regulatory approvals

None

## Rilpivirine (RPV)

### Class(es)

Not provided

### Development stage

Pre-clinical

### Clinical trial number(s)

None

### Foreseen/approved indication(s)

Not provided

### Foreseen user group

Not provided

### Foreseen duration between application(s)

Not provided

### Applications to Stringent Regulatory Authorities (SRA) / regulatory approvals

None

## Rilpivirine (RPV), Dolutegravir (DTG)

### Class(es)

Antiretrovirals

### Development stage

Pre-clinical

### Clinical trial number(s)

None

### Foreseen/approved indication(s)

HIV PrEP/ART

### Foreseen user group

PLHIV and people at risk of HIV

### Foreseen duration between application(s)

6 months

### Applications to Stringent Regulatory Authorities (SRA) / regulatory approvals

None

## Cabotegravir (CAB)

### Class(es)

Not provided

### Development stage

Not provided

### Clinical trial number(s)

Not provided

### Foreseen/approved indication(s)

Not provided

### Foreseen user group

Not provided

### Foreseen duration between application(s)

Not provided

### Applications to Stringent Regulatory Authorities (SRA) / regulatory approvals

Not provided

# Patent info

## Technology patent families

### Patent informations

| Patent description | Representative patent | Categories | Patent holder | Licence with MPP | Patent source |
|---|---|---|---|---|---|
| Polymeric implants with high drug loading and long-acting drug release<br>Expiry date: 2040-01-31<br>Disclosed herein are polymeric implants and controlled release drug delivery systems to provide high drug loading and long-acting drug release. Provided herein are methods for making the same. Methods of administering pharmacologically active agents via the disclosed polymeric implants and controlled release drug delivery systems are also provided. | WO2020160379 | | THE UNIVERSITY OF NORTH CAROLINA AT CHAPEL HILL | No | World Intellectual Property Organization |

### Patent status

| Patent status/countries | Low, Low- middle and upper-middle | High income |
|---|---|---|
| Granted | | |
| Filed | | United States of America |
| Not in force | World Intellectual Property Organization (WIPO) | World Intellectual Property Organization (WIPO) |

### MPP Licence(s)

# Cabotegravir (LAI candidate)

## Patent informations

| Patent description | Representative patent | Categories | Patent holder | Licence with MPP | Patent source |
|---|---|---|---|---|---|
| Dolutegravir and Cabotegravir compounds<br>Expiry date: 2026-04-28<br>The present invention is to provide a novel compound (I), having the anti-virus activity, particularly the HIV integrase inhibitory activity, and a drug containing the same, particularly an anti-HIV drug, as well as a process and an intermediate thereof. Compound (I) wherein Z<1> is NR<4>; R<1> is hydrogen or lower alkyl; X is a single bond, a hetero atom group selected from O, S, SO, SO2 and NH, or lower alkylene or lower alkenylene in which the hetero atom group may intervene; R<2> is optionally substituted aryl; R<3> is hydrogen, a halogen, hydroxy, optionally substituted lower alkyl etc; and R<4> and Z<2> part taken together forms a ring, to form a polycyclic compound, including e.g., a tricyclic or tetracyclic compound. | WO2006116764 | Compound | Glaxosmithkline Llc | Yes | US FDA, Health Canada |

## Patent status

| Patent status/countries | Low, Low- middle and upper-middle | High income |
|---|---|---|
| Granted | Brazil, China, Morocco, Mexico, Philippines, Ukraine, Viet Nam, South Africa, Türkiye, Armenia, Azerbaijan, Belarus, Kyrgyzstan, Kazakhstan, Moldova, Republic of, Tajikistan, Turkmenistan, Nigeria, Colombia, Indonesia, Malaysia, Algeria | United States of America, Australia, Canada, Cyprus, Hong Kong, Israel, Japan, Korea, Republic of, Luxembourg, Norway, New Zealand, Taiwan, Province of China, Austria, Belgium, Bulgaria, Switzerland, Czechia, Germany, Denmark, Estonia, Spain, Finland, France, United Kingdom, Greece, Hungary, Ireland, Iceland, Italy, Liechtenstein, Lithuania, Latvia, Monaco, Netherlands, Poland, Portugal, Romania, Sweden, Slovenia, Slovakia, |

| Patent status/countries | Low, Low- middle and upper-middle | High income |
|---|---|---|
| Filed | Egypt | United States of America, Cyprus, Luxembourg, Norway, Finland, France, Hungary, Lithuania, Netherlands, Slovenia |
| Not in force | Türkiye, India, World Intellectual Property Organization (WIPO) | United States of America, Cyprus, Hong Kong, Israel, Japan, Luxembourg, Austria, Belgium, Bulgaria, Switzerland, Czechia, Germany, Denmark, Estonia, Spain, Finland, France, United Kingdom, Greece, Hungary, Ireland, Iceland, Italy, Liechtenstein, Lithuania, Latvia, Monaco, Netherlands, Poland, Portugal, Romania, Sweden, Slovenia, Slovakia, World Intellectual Property Organization (WIPO) |

## MPP Licence(s)

**MPP Licence on Cabotegravir (tablet form and/or long-acting injectable form) for HIV pre-exposure prophylaxis (PrEP)**

https://medicinespatentpool.org/licence-post/cabotegravir-long-acting-la-for-hiv-pre-exposure-prophylaxis-prep

## Patent informations

| Patent description | Representative patent | Categories | Patent holder | Licence with MPP | Patent source |
|---|---|---|---|---|---|
| Cabotegravir processes and intermediates<br>Expiry date: 2031-03-22<br>Relates to the preparation of carbamoylpyridone derivatives and intermediates which are useful as HIV integrase inhibitors. | WO2011119566 | Intermediate(s), Process | Glaxosmithkline Llc, Goodman, Steven N, Kowalski, Matthew, Mans, Douglas, Wang, Huan | Yes | MPP search |

## Patent status

| Patent status/countries | Low, Low- middle and upper-middle | High income |
|---|---|---|
| Granted | China, Albania, Serbia, Bosnia and Herzegovina, Montenegro, Türkiye, North Macedonia, India | Liechtenstein, Italy, Norway, Malta, Denmark, Belgium, United Kingdom, Greece, Netherlands, Hungary, Croatia, Switzerland, Spain, San Marino, Slovenia, Austria, Romania, Iceland, Cyprus, Finland, France, Bulgaria, Slovakia, Poland, Latvia, Ireland, Estonia, Germany, Luxembourg, Portugal, Czechia, Lithuania, Monaco, Sweden, Japan, Korea, Republic of, United States of America |
| Filed | | Singapore, Taiwan, Province of China |
| Not in force | World Intellectual Property Organization (WIPO) | World Intellectual Property Organization (WIPO) |

## MPP Licence(s)

**MPP Licence on Cabotegravir (tablet form and/or long-acting injectable form) for HIV pre-exposure prophylaxis (PrEP)**

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# Supporting material

## Publications

** <a href="https://pubmed.ncbi.nlm.nih.gov/34216767/" rel="noopener noreferrer" target="_blank">Biodegradable polymeric solid implants for ultra-long-acting delivery of single or multiple antiretroviral drugs</a> <br> Panita Maturavongsadit, Roopali Shrivastava, Craig Sykes, Mackenzie L. Cottrell, Stephanie A. Montgomery, Angela D.M. Kashuba, S. Rahima Benhabbour, <br> International Journal of Pharmaceutics, Volume 605, 2021,120844, ISSN 0378-5173, https://doi.org/10.1016/j.ijpharm.2021.120844. <br> (https**

Lack of adherence is a key barrier to a successful human immunodeficiency virus (HIV) treatment and prevention. We report on an ultra-long-acting (ULA) biodegradable polymeric solid implant (PSI) that can accommodate one or more antiretrovirals (e.g., dolutegravir (DTG) and rilpivirine (RPV)) at translatable human doses (65% wt.) in a single implant. PSIs are fabricated using a three-step process: (a) phase inversion of a drug/polymer solution to form an initial in-situ forming solid implant, (b) micronization of dried drug-loaded solid implants, and (c) compression of the micronized drug-loaded solid powder to generate the PSI. DTG and RPV can be pre-combined in a single PLGA-based solution to make dual-drug PSI; or formulated individually in PLGA-based solutions to generate separate micronized powders and form a bilayer dual-drug PSI. Results showed that in a single or bilayer dual-drug PSI, DTG and RPV exhibited physicochemical properties similar to their pure drug analogues. PSIs were well tolerated in vivo and effectively delivered drug(s) over 180 days with concentrations above 4× PA-IC90 after a single subcutaneous administration. While biodegradable and do not require removal, these PSIs can safely be removed to terminate the treatment if required. The versatility of this technology makes it attractive as an ULA drug delivery platform for HIV and various therapeutic applications.

Keywords: Polymeric solid implants; Long-acting drug delivery; Poly(lactic-co-glycolic acid) (PLGA); Dolutegravir; Rilpivirine; HIV prevention

** <a href="https://www.ncbi.nlm.nih.gov/pmc/articles/PMC7773589/" rel="noopener noreferrer" target="_blank" style="color: rgb(48, 48, 48);">A new engineering process of biodegradable polymeric solid implants for ultra-long-acting drug delivery. </a> Maturavongsadit, P., Paravyan, G., Kovarova, M., Garcia, J. V., & Benhabbour, S. R. (2020). International journal of pharmaceutics: X, 3, 100068. https://doi.org/10.1016/j.ijpx.2020.100068 **

We present a long-acting (LA) biodegradable polymeric solid implant (PSI) fabricated using a new process combining in-situ phase inversion and compression. This robust process allows fabrication of solid implants that can have different shapes and sizes, accommodate high drug payloads, and provide sustained drug release over several months. Herein the integrase inhibitor dolutegravir (DTG) was used to develop PSIs for HIV prevention. PSIs were fabricated using a three-step process by (a) phase inversion of DTG-loaded polymer solution to form an initial in-situ forming implant in an aqueous solution, (b) micronization of dried DTG-loaded solid implants, and (c) compression of the micronized DTG-loaded solid implants to form the PSI. High drug loading (up to 85 wt%) was achieved in the PSIs. DTG exhibited minimum burst release in the first 24 h (<6%) and sustained release kinetics over 6 months. The release kinetics of DTG can be fine-tuned by varying drug-loading concentration, the ratio of polymer (poly(lactic-*co*-glycolic acid), PLGA) to solvent (*N*-methyl-2-pyrrolidone, NMP) and polymer (PLGA) molecular weight in the precursor solution. The physical/chemical properties of DTG were retained post-storage under accelerated storage conditions (40 °C/75% relative humidity) for 6 months. The versatility of this technology makes it an attractive drug delivery platform for HIV prevention applications.

**Keywords:** Solid implants, In-situ, Phase inversion, Compression, Long-acting drug delivery, Poly(lactic-*co*-glycolic acid), HIV prevention

## Additional documents

No documents were uploaded

## Useful links

- Benhabbour lab research projects

# Access principles

## Collaborate for development

Consider on a case by case basis, collaborating on developing long acting products with potential significant public health impact, especially for low- and middle-income countries (LMICs), utilising the referred to long-acting technology

Not provided

## Share technical information for match-making assessment

Provide necessary technical information to a potential partner, under confidentiality agreement, to enable preliminary assessment of whether specific medicines of public health importance in LMICs might be compatible with the referred to long-acting technology to achieve a public health benefit

Not provided

## Work with MPP to expand access in LMICs

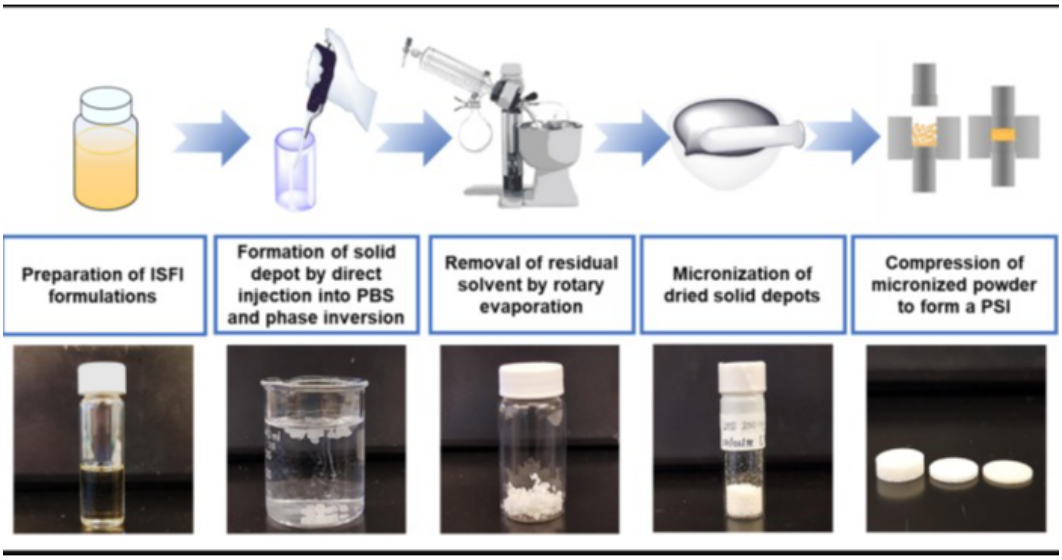
In the event that a product using the referred to long-acting technology is successfully developed, the technology IP holder(s) will work with the Medicines Patent Pool towards putting in place the most appropriate strategy for timely and affordable access in low and middle-income countries, including through licensing

Not provided

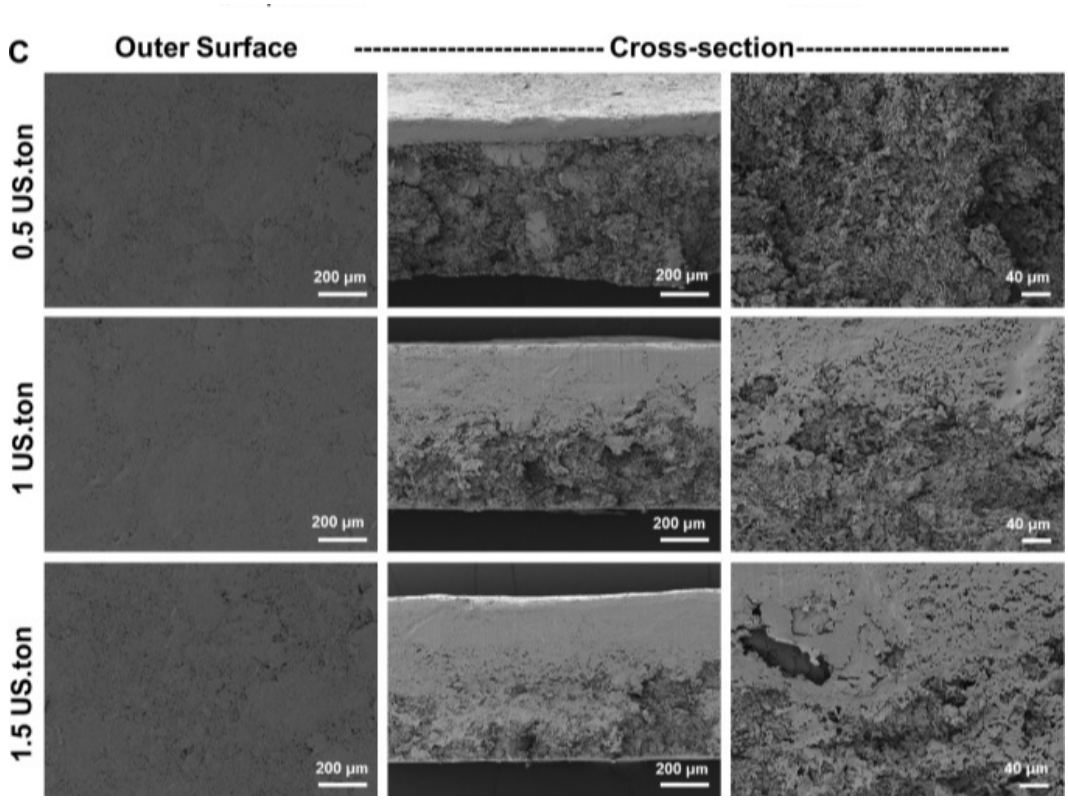
# Comment & Information

Our research at the Benhabbour Lab focuses on engineering novel tunable delivery platforms and polymer-based devices that can treat or prevent a disease. Our work combines the elegance of polymer chemistry with the versatility of engineering and formulation development to design and fabricate efficient and translatable delivery systems for a wide range of applications including cancer treatment, HIV prevention, osteoporosis and regenerative medicine.

# Illustrations




PSI preparation process by a combination of phase inversion and tablet compression techniques




PSI microstructure: SEM images representing cross-section images of placebo PSIs fabricated with varying compression forces