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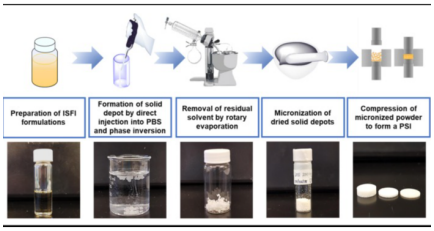

Tunable Biodegradable Ultra-Long-Acting Polymeric Solid Implant (PSI)

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

-

-

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 Expiry date: 2040-01-31 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 Expiry date: 2026-04-28 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 Expiry date: 2031-03-22 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		San Marino, Singapore, Taiwan, Province of China
Not in force	World Intellectual Property Organization (WIPO)	World Intellectual Property Organization (WIPO)

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Supporting material

Publications

** Biodegradable polymeric solid implants for ultra-long-acting delivery of single or multiple antiretroviral drugs
 Panita Maturavongsadit, Roopali Shrivastava, Craig Sykes, Mackenzie L. Cottrell, Stephanie A. Montgomery, Angela D.M. Kashuba, S. Rahima Benhabbour,
 International Journal of Pharmaceutics, Volume 605, 2021,120844, ISSN 0378-5173, https://doi.org/10.1016/j.ijpharm.2021.120844.
 (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 new engineering process of biodegradable polymeric solid implants for ultra-long-acting drug delivery. 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

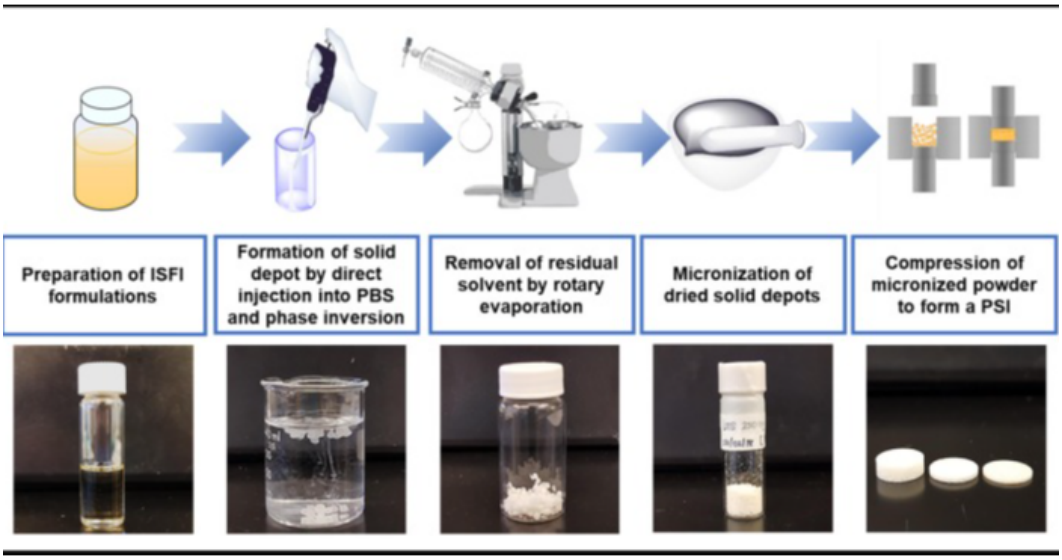
In the event that a product using the referred to long-acting technology is successfully developed, the technology IP holder(s) will work with the Medicines Patent Pool towards putting in place the most appropriate strategy for timely and affordable access in low and middle-income countries, including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

Not provided

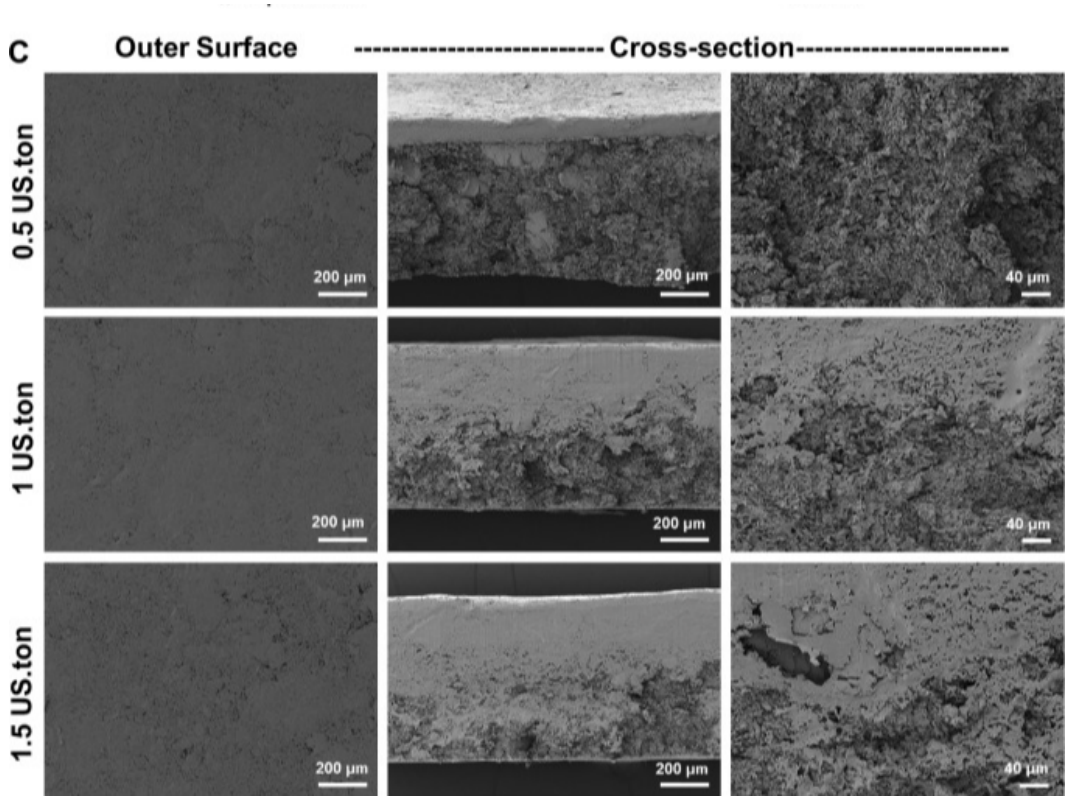
Comment & Information

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