A Novel Approach to tackle Osteoarthritis:

Engineering a self-administrable tissue regenerative transdermal patch for articular cartilage growth and inflammation alleviation

BACKGROUND

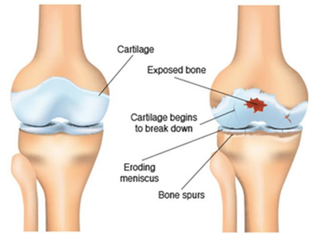


Image taken from Altair Health

Osteoarthritis affects 7% of the global population, more than 500 million worldwide. Current treatment options such as medicines, joint injections, or total knee replacement only help to temporarily mitigate the pain and inflammation.

There is a NEED for a therapy that can restrict structural deterioration of cartilage and enable tissue regeneration

PREVIOUS RESEARCH

Hypothesis: My injection consisting of nanosized hydrogel polymers, Sclerotin protein, collagen proteoglycans, and hyaluronic acid, will alleviate pain and inflammation, slow down current cartilage degradation, and stimulate new articular cartilage growth, restoring the knee to its healthy state.

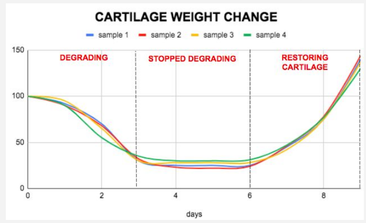
CARTILAGE WEIGHT CHANGE

Graph made by me

Phase 1:
Drop in weight due to water loss

Phase 2:
Moisture is retained due to Polyzene - F hydrogel polymers

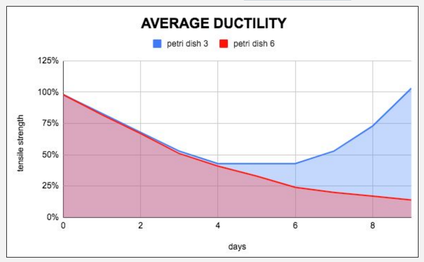
Phase 3:
Collagen Proteoglycan restores cartilage weight



***note: cartilage size differed per phase, so weight was sized up relative to 100 g**

Graph made by me

DUCTILITY



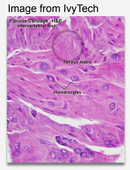
Phase 1:
Linear decay in tensile strength due to cartilage degradation → collagen proteoglycan levels dropped

Phase 2:
Steady/no-change in graph when Polyzene - F hydrogel polymers are added

Phase 3: The tensile biomechanical properties of cartilage mainly relate to the cross-linked collagen network of the extracellular matrix. Therefore, when extra collagen was added to the cartilage, it increased the tensile strength and tissue development.

ELASTICITY

Image from IvyTech



- Elastic modulus and fibril lengths decreased as cartilage degraded during the first 3 days
- Decreases in the elastic modulus decreased ability of cartilage to store elastic energy. This led to cartilage fibrillation and fissure formation
- With the addition of collagen proteoglycan, fibril lengths and overall elasticity increased

My experiment successfully slowed down current cartilage degradation, stimulated new articular cartilage growth, and improved elasticity and mobility of cartilage due to increased elastic modulus and increased fibril lengths. However, alleviating pain and inflammation, decreasing friction between cartilage, and restoring the knee to its healthy state were not measurable goals.

IMPROVEMENTS FROM LAST YEAR

Most biotherapeutics are injected using a hypodermic needle. Last year, I chose to create a formula for an injection due to its low-cost, rapid, and direct way to deliver almost any type of molecule into the body. However, hypodermic needles cannot be easily used by patients themselves and are therefore utilized primarily in the clinic or at home by patients who have received special training on correct injection method, safe needle disposal, and other issues. This year, I want to extend the route of administration so this formula can be more accessible and self-administrable.

ENGINEERING GOAL

I hope to create a microneedle transdermal patch that is biocompatible and can successfully slow down current cartilage degradation and stimulate new articular cartilage growth.
(as the formula did in vitro last year).

PATCH GOALS:

- Dissolvable Microneedles
- Self- Administered
- Biodegradable
- No Refrigeration
- Long Shelf Life
- Comfortable

RESEARCH

I conducted research to find an ideal patch to satisfy all my patch goals:

1) To make the formula have a long shelf life and no refrigeration period, the formula would be lyophilized.
2) To make the microneedles dissolvable, the membrane of the microneedles would be made of CLDN1 to disrupt the tight junctions on the epithelial cell lining 16HBE. This disruption is a critical step in antigen responsiveness and will be measured by increased transepithelial water loss and increased antigen specific antibodies in the PBPK modeling software.
3) After considering various synthetic biodegradable polymers and eco-friendly materials, to make the patch biodegradable, the patch would comprise of Bamboo Fibre, Aloe Vera, Oil, Activated Charcoal.
4) To create a comfortable patch, I researched different configurations to find the most comfortable design for a knee. A U-shaped patch with 1 cm 3M Biodegradable Polycarbonate adhesive would work best.

PROCEDURE

MoBi is a software tool for physiological modeling and simulation. To test the reaction CLDN-1 microneedles would have on epithelial skin cells, I entered parameters describing the skin, ambient conditions, experimental conditions, the permeant, and dosage conditions.

The simulation of the model returns:
- amounts of permeant present at different skin depths, over the time of the simulation
- the amount of permeant that has escaped the vehicle and skin through evaporation
- the cumulative amount and the flux, over time, of permeant that has crossed the entire skin membrane (for in vitro simulations) or cleared the dermis into the bloodstream (for in vivo simulations)

Permeant properties	
Molecular weight MW	336.47
log $K_{o/w}$	4.05
Solubility S_w	
C atoms	22
Br atoms	0
Cl atoms	0
F atoms	6
H atoms	28
N atoms	2
O atoms	2
P atoms	0
S atoms	0
I atoms	0
Permeant includes other elements	0
Number of double bonds	7
Number of triple bonds	0
Number of rings	3
Compound type	0
Use experimental permeant density	1
Temperature at experimental permeant density	25
Experimental permeant density	1.09
Grain class	2
Boiling temperature	466
Use experimental permeant water solubility	1
Temperature at experimental permeant water solubility	25
Experimental permeant water solubility	24
Melting temperature	88
Use strongest acid pK_a	0
Strongest acid pK_a	0
Use strongest base pK_a	1
Strongest base pK_a	8.9
Vapor pressure	0

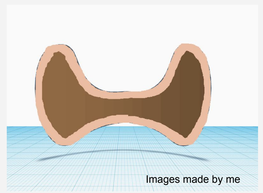
Application properties	
Dose	24
Area of application	1
Wind velocity	16.8
Occluded vehicle	1
Vehicle type	1
Volatile vehicle	0
Vehicle pH	7.4
Vehicle volume	0.472

[Image from MoB software]

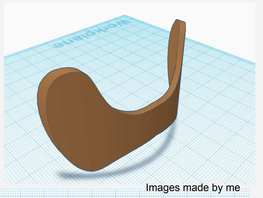
Running a simulation using MoBi model
- Open Skin Permeation Model in MoBi and set skin spatial structure properties *(pictured left)*
- Extract CLDN1 chemical properties from MobiDB. Import into Pk-Sim and subsequently MoBi after creating compound
- Set dosage and vehicle properties
- Run simulation of:
  - CLDN1 absorption & measure epithelial water loss
    - CLDN1 cleared (dermis -> bloodstream)
    - Rate of clearance
  - Drug permeability and delivery
- Connect skin permeation model to whole body model. Repeat process.

RESULTS

PATCH DETAILS



Images made by me



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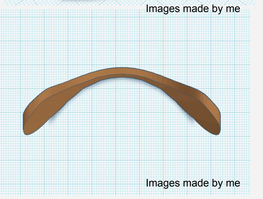
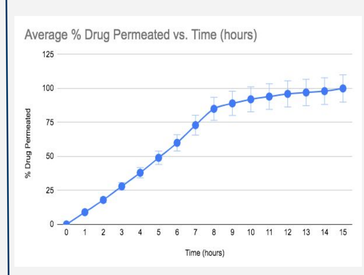
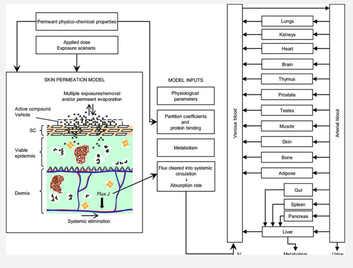


Images made by me

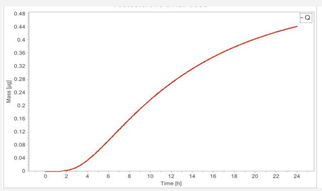
- Patch material: Bamboo Fibre, Aloe Vera, Oil, Activated Charcoal
- Microneedle dimensions: 24 microneedles, 3mm x 1.5 mm
- Microneedle material: CLDN-1 membrane
- Patch shape: U-shape
- Patch Thickness: 2 mm thickness
- Dosage of formula: 100 µmol
- Placement of the patch: wrapped around knee cap lyophilized formula
- Storage requirements: 1 year storage life + no refrigeration
- Adhesive: 1 cm of 3M Biodegradable Polycarbonate adhesive around the patch

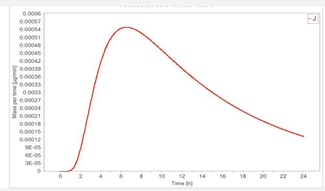
MoBI RESULTS





[Image made by me] **Left**: % of Drug permeation over time [Image from Open Source Pharmacology MoB] **Right**: Model architecture





[Images from MoBi] **Left**: Simulation of the cumulative dermis to bloodstream clearance amount Q of CLDN1 **Right**: Rate of clearance J during the course of the experiment. 0.53 µg.cm-2 over 1 cm2 of partially hydrated skin

CONCLUSION

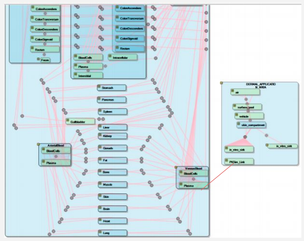
I achieved the following Engineering Goals:

- The patch + drug is biocompatible with a host
- Dissolvable Microneedles (DMN) release transepithelial water loss to reconstitute with lyophilized formula and release into the skin
- Self-Administrable
- No Refrigeration
- Long Shelf Life
- Biodegradable

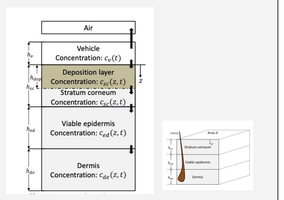
However, the following goals were not quantifiable:

- Comfort
- Indication of inflammation alleviation from MoBi software
- Accessibility

MODEL + SIMULATION



[Image from MoBi] Full MoBi model topology for integrating Skin and full-body for in-vivo simulation



[Images from MoBi] The diffusion of permeant from one sub-sub-layer to another is numerically computed using the method of finite differences and Fick's law, which models the one-dimensional diffusive flux J (amount per unit area per unit time) at spatial position z, at time t, in the direction of increasing z as $J(z,t) = -D\,\partial c(z,t)/\partial z$,

REAL WORLD APPLICATION

The discovery that a formula consisting of nanosized hydrogel polymers, sclerotin protein, and collagen proteoglycans in the form of a transdermal patch could help stop cartilage degradation and stimulate the growth of articular cartilage is a huge lead in the field of OA that needs to be heavily studied and developed on to find more concrete evidence on the positive benefits of such a therapy. Due to our aging population and our obesity epidemic, in addition to the 500 million people worldwide with OA, millions more will continue to develop OA, and there is an immediate need for new therapies to stop or reverse this debilitating disease.

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