Physicochemical Investigations Of A Drug Delivery Oscillator

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Purpose: To identify the factors that prevent sustained oscillations of constant period and amplitude in a glucose-driven hormone delivery device. **Methods:** The glucose-driven chemomechanical oscillator is a side-by-side transport cell. The cell's chambers are separated by a poly(*N*-isopropyl acrylamide-co-methacrylic acid) [poly (NIPA-*co*-MAA)] hydrogel membrane, which undergoes swelling and shrinking in response to change in pH. Saline containing constant glucose concentration flows through donor cell at pH=7.4. The receptor cell contains enzymes-glucose oxidase and catalase along with a piece of marble, which acts as a proton shunt. pH change is followed in the receptor cell over time to demonstrate oscillations. The oscillations slow down with time; the period increases while the amplitude decreases with time. Gluconic acid/gluconate buffer build-up in the receptor cell resists pH change. Calcium ion build-up (from marble) affects the swelling behavior of membrane. The buffer build-up is investigated by removing aliquots from receptor cell solution during oscillations and determining its buffer capacity. Effect of calcium ions is investigated by spiking calcium chloride in receptor cell solution during course of oscillations. Also, effect of calcium ions on oscillations is monitored by successively increasing concentration of calcium chloride in the environment surrounding the hydrogel. **Results:** Henderson-Hasselbach titration curves for gluconic acid/gluconate buffer are generated. During oscillations, the buffer capacity increases with time. As buffer builds-up, the periodicity of oscillations increases and their amplitude decreases. The oscillations are completely quenched in presence of calcium chloride. In accordance to Donnan theory, calcium build-up affects the electroneutrality and ionic osmotic pressure, thus affecting membrane swelling. **Conclusions:** Gluconic acid/gluconate buffer build-up affects the periodicity and amplitude of oscillations in the hydrogel/enzyme based oscillator. Calcium ions do play a retarding role as well. Future work involves the elimination of these factors to obtain sustained oscillations of constant periodicity and amplitude.

Introduction

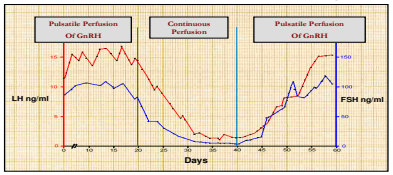
Hypogonadotropic Hypogonadism

Cause: Failure of endogenous pulsatile **Gonadotropin Releasing Hormone (GnRH)** secretion

Effect: Failure to reach puberty in males
Failure of reproductive cycle in females

Treatment: Pulsatile delivery of GnRH with an external pump (12 doses/day)

Pulsatile vs. Continuous Delivery



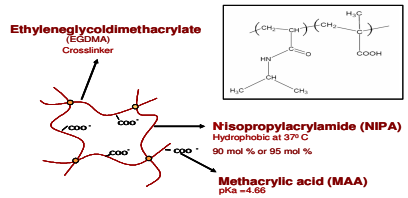
Responses of LH & FSH levels to pulsatile & continuous infusion of GnRH

Belchetz, P. E.; T.M. Plant; E. J. Keogh; E. Knobil *Science* 1978 202: 631-633

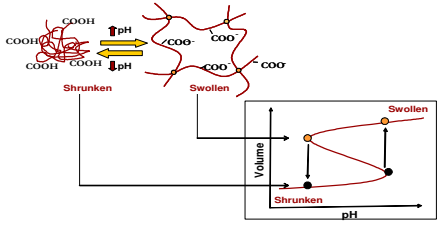
Proposed Device: Glucose powered hydrogel-based autonomous system

Device Membrane - Hydrogel

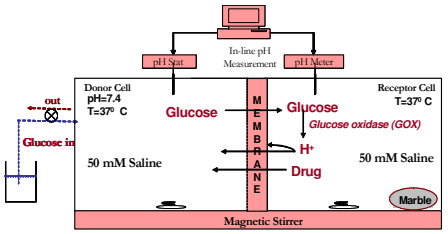
Hydrogel Membrane Chemistry



Volume Phase Transition



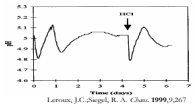
Device Setup & Operation



1. Glucose (in 50 mM saline) easily enters device chamber through swollen membrane, reacts with GOX to produce protons. Drug molecules are released into external environment
2. Protons diffuse into membrane causing collapse ---- consequently, glucose influx and drug efflux stops
3. Protons diffuse out of membrane causing it to swell again.
4. System is poised to repeat step 1.

Role of Marble

- **Without Marble**
  Days required to traverse the hysteresis band
  At most a pair of oscillations before pH converged to stationary value

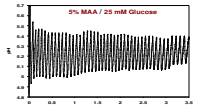


Leroux, J.C.;Siegel, R. A. *Chaos* **1999**,9,267

- **With Marble**
  Marble accelerates pH swing
  Pseudo First Order Rate Constant

$$\frac{dH^+}{dt} = -k_{app}[H^+]$$

$$2H^+ + CaCO_3 \rightarrow Ca^{2+} + H_2O + CO_2\uparrow$$



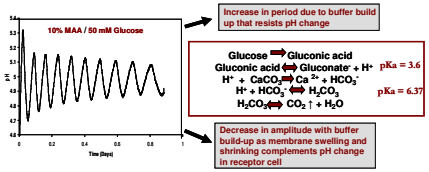
Oscillatory Behavior Not Sustained

- Oscillation periodicity increases and amplitude decreases with time
- Oscillations stop after few days
- It is necessary to identify and eliminate factors that prevent sustained oscillations of constant periodicity and amplitude

Hypothesis

Factors Preventing Sustained Oscillations

- **Buffer Build-Up Affects Oscillation Frequency & Amplitude**



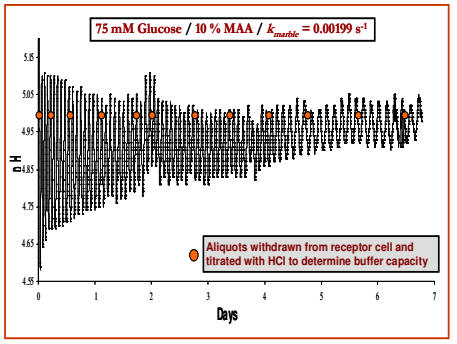
- **Calcium Ions (from marble) Affects Membrane Swelling**

$$\Delta\pi = \frac{RT\,\omega_f^2}{4I}$$

$\Delta\pi$: Donnan Osmotic Pressure
ω_f : Molar fixed charge density of hydrogel
I : Ionic strength of receptor cell solution

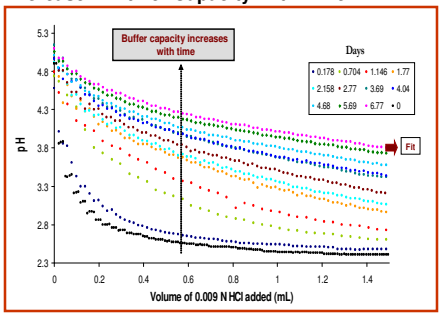
Experiment

Investigating Buffer Capacity

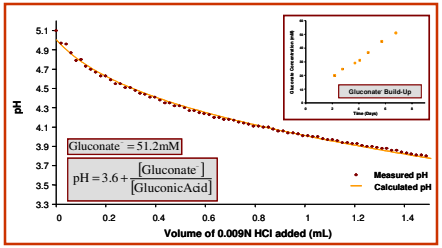


Experimental Results

Increase in Buffer Capacity With Time

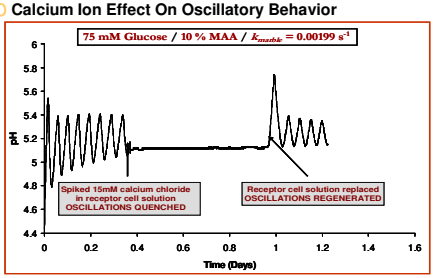


Gluconate⁻/Gluconic Acid Equilibrium - Henderson-Hasselbach Model At 6.77 Days

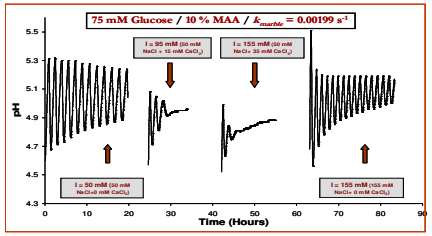


Experimental Results

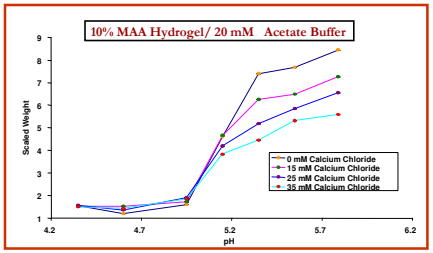
Calcium Ion Effect On Oscillatory Behavior



Calcium Ion Concentration Effect On Oscillations



Calcium Effect On Swelling Behavior of Oscillator Gel



Conclusions

- Gluconic acid/gluconate buffer build up in the receptor cell slows down pH oscillations by increasingly resisting change in pH
- Calcium ion build-up (from marble) affects swelling behavior of the membrane and is responsible for cessation the oscillations
- Future work is to eliminate these factors to obtained sustained oscillations of constant periodicity and amplitude.

Acknowledgements

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