Equivalence of Complex Products
Cyclosporine Ophthalmic Emulsion

Robert A. Bellantone, Ph.D.

President, Physical Pharmaceutica LLC

PhysPharm
Physical Pharmaceutica

Ophthalmic emulsions as complex dosage forms

- Two marketed products (cyclosporine 0.05% and difluprednate 0.05%)

- Ophthalmic emulsions are complex materials
  - Drug is distributed in several phases
  - Complex set of conditions governing release

- Ophthalmic emulsions are subject to a complex route of delivery
  - The formulation and target region can affect each other
  - Special considerations for ocular delivery

- Two special considerations must be taken into account
  - Short residence time in the ocular region
  - Administration leaves a thin film of formulation on the ocular surfaces (~50 micron)
    - Thin film does not act as a drug depot– % depletion per time is large
    - Formulation temperature goes to ~35 °C (ocular surface temp) in about 1 second
    - *The film thickness is a critical factor affecting in vitro release testing*

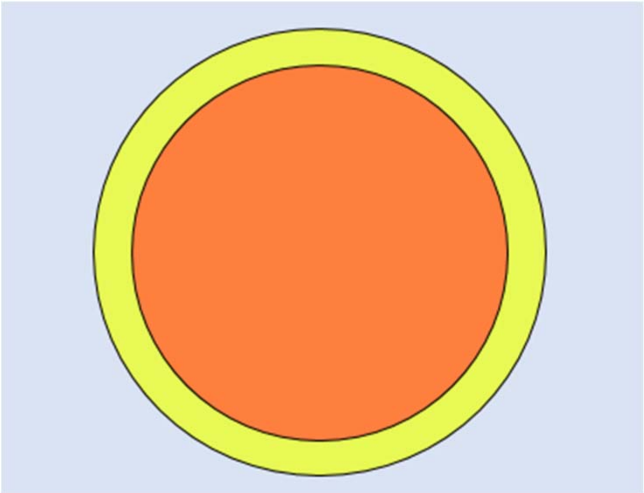
- Cyclosporine property: as formulation temperature increases from storage temp to 35 °C, cyclosporine solubility decreases in water but increases in globules

Cyclosporine ophthalmic emulsions

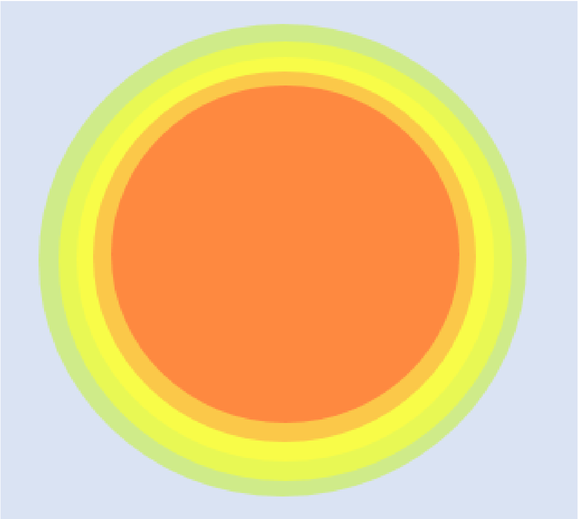
- Microemulsion
  - Globule size ~ 100-200 nm, globules occupy ~2% of the formulation volume
  - Surface to surface separation ~250-500 nm
  - In 0.1 mL, 5-40 x 10^{11} globules with total surface area ~600-1200 cm^2
  - In a 50 micron film, estimate about 1% of globules are within 500 nm of ocular surfaces

- Structure likely affected by geometry and miscibility of Tween 80 and castor oil

If pure Tween-80, surfactant layer thickness would be 10-20 nm (~10-20 molecules)



"Surfactant layer" may be more like a transition layer from oil to water due to miscibility



Comparing ophthalmic emulsions

- If two ophthalmic emulsion formulations are “equivalent”, they will perform in the same way when administered in vivo

- One approach: two formulations will perform equivalently in vivo if they
  - Start out the same (same during storage– static measurements)
  - Respond in the same way to in vivo perturbations (kinetic processes)

- Starting state reflects storage conditions, static parameter measurements

- Response– process(es) induced by perturbations encountered in vivo
  - Rapid temperature change, redistribution and drug loss by absorption
  - Other possible factors (tearing related, for instance)
  - These perturbations are <u>large</u> and <u>occur rapidly</u> (thin film effects)

Factors affecting drug availability vs. time

- Contact time in the ocular region
  - Globule size and surface area
  - Formulation viscosity
  - Surface interactions
  - Tearing (pH, osmolality)
- Drug availability to tissue vs. time (transfer)
  - Initial distribution
  - Release kinetics from globule phases
  - Tearing and dilution

- Parameters to measure (static, initial conditions)
  - Globule size (contact area, surfactant distribution)
  - Viscosity, zeta potential, surface tension
  - Tearing (pH, osmolality)
  - Distribution of the drug in the formulation

- Processes that follow a change in environment (kinetic response)
  - IVRT (in vitro release test)
  - Measure release of drug in the presence of a sudden temperature change

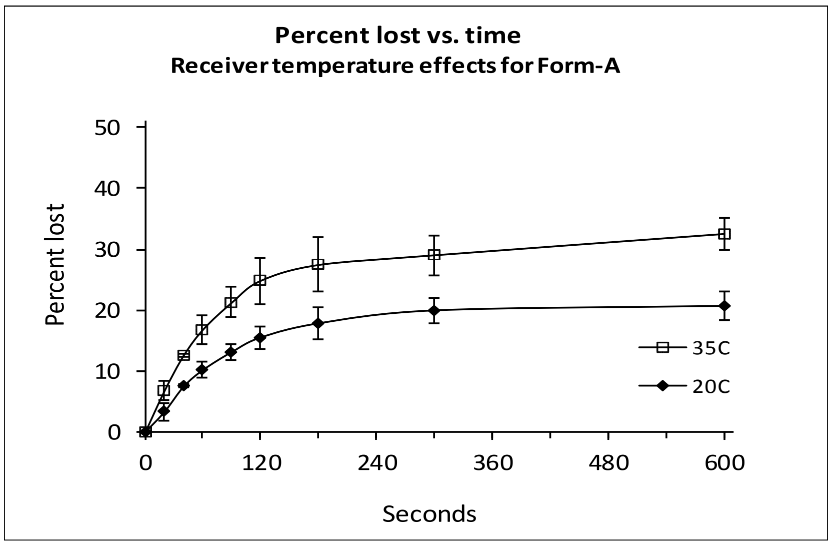
- Data supports that all of the above are necessary– cannot theoretically relate the variables to reduce the measurement set

Release of cyclosporine from ophthalmic emulsions

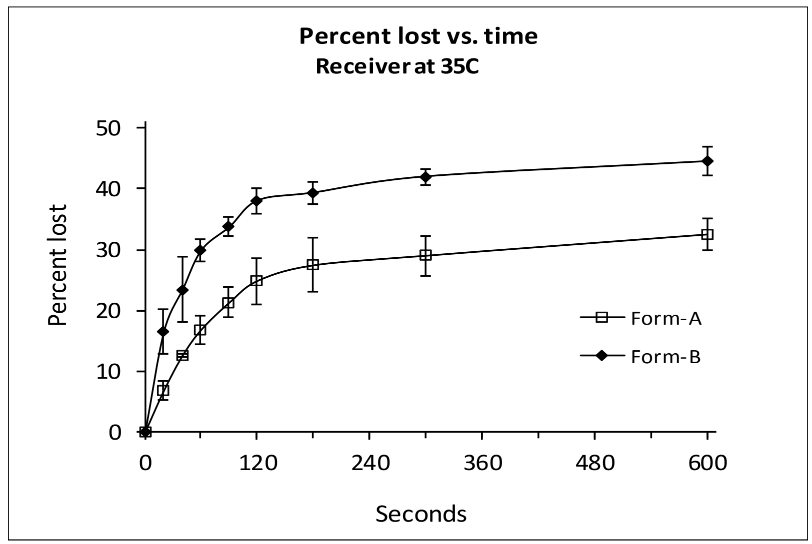
- Two Q1/Q2 formulations (Form-A and Form-B) produced by different processes
- Looked at effect of temperature change, and effect of processing method
- Release measured using pulsatile microdialysis (PMD)

- See biphasic patterns. We think that
  - Drug in aqueous phase is immediately available to ocular tissues
  - Drug in globules takes longer to partition into ocular tissues
  - In vitro release data shows biphasic release patterns

Form-A release into receivers at 20 and 35 ℃



Form-A vs. Form-B release into receivers at 35 ℃



Note: 100% release corresponds to ~2.85 μg/cm^2 for all plots

Comments on comparative in vitro release tests

An ideal in vitro release test accounts for factors relevant to the in vivo conditions

- The ocular residence time is short
  - Release test should obtain data in a timeframe similar to the ocular residence time
  - Should avoid extrapolation of data from long times to short times
- Test should expose the formulation to perturbations from the stored state that are similar in magnitude and timescale to in vivo perturbations
  - Formulation increases temperature from 20 to 35 °C (nominally) nearly instantly
  - In the ocular region, large fraction of drug lost per time– affects diffusion and redistribution

Observation: Typical in vitro release rate tests (example, Franz cells) are far from ideal

- Release data are typically obtained over hours and require extrapolation to early times
  - Data typically obtained from 30 minutes to hours, so must extrapolate close to time = 0
  - Extrapolation requires a model with intercept = 0 (M vs. t, M vs. $t^{0.5}$, or ???)
  - If uncertainties in the intercept are not small compared to the differences in formulations, extrapolation cannot discriminate at the early (relevant) times
- Release experiment reflects a much more gentle and slow perturbation than occurs in vivo
  - Cannot raise temperature instantly, so perform constant temperature experiment
  - Fraction released per time is slow because of depot effect (formulation layer >> 50 microns)

Summary

- Ophthalmic emulsions are complex
  - Complex form of matter
  - Complex interactions with the ocular environment when administered in vivo
  - Cyclosporine is particularly difficult due to solubility properties

- The complexity makes it difficult (if possible at all) to model drug delivery

- We like the “same starting state” and “same response” approach

- Starting state: Static parameters to measure before administering the drug
- Response: release kinetics induced by changes reflective of those incurred in vivo

- All of the above are candidates for further research
  - Mechanistic studies of what affects release are feasible
  - Mechanistic studies of how formulation process affects the final product are more difficult

Thank you.

This work was funded in part by FDA Contract HHSF223201610105C.
We gratefully acknowledge this support.

Thanks to Piyush G. Patel, Ph.D. and Kosha B. Shah, Ph.D.

PHYSPHARM
Physical Pharmaceutica