Equivalence of Complex Products Cyclosporine Ophthalmic Emulsion

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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*

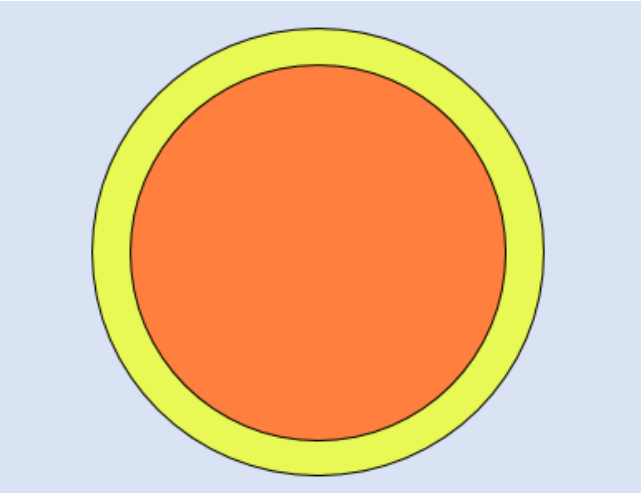
- Cyclosporine property: as formulation temperature increases from storage temp to 35 °C, cyclosporine solubility decreases in water but increases in globules

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 large and occur rapidly (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

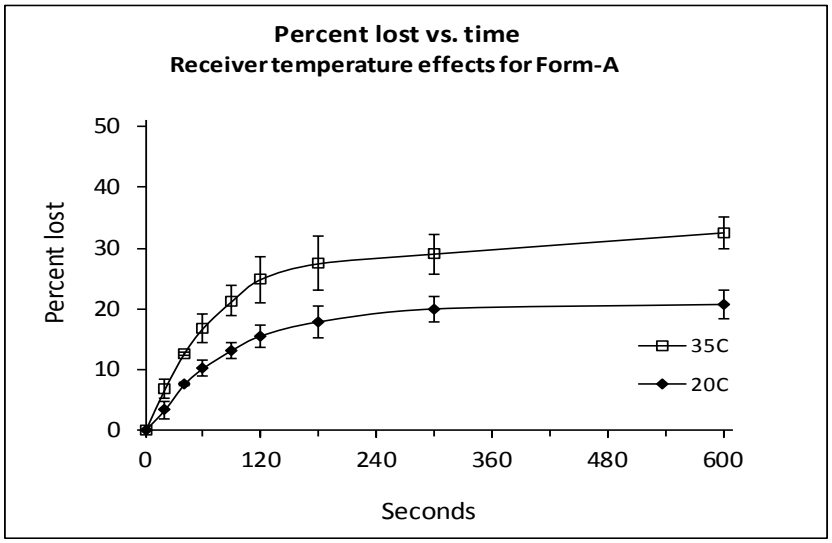
- Data supports that all of the above are necessary– cannot theoretically relate the variables to reduce the measurement set

Release of cyclosporine from ophthalmic emulsions

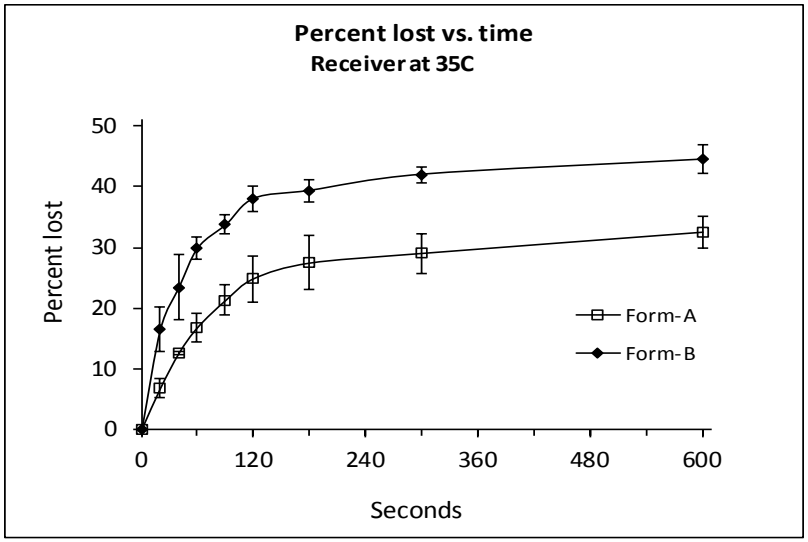
- Two Q1/Q2 formulations (Form-A and Form-B) produced by different processes
- Looked at effect of temperature change, and effect of processing method
- Release measured using pulsatile microdialysis (PMD)

- 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

R. Bellantone, May 2017

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

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