

# COMPLEXITY OF INVITRO DRUG RELEASE MEASUREMENTS FOR OPHTHALMIC DRUG PRODUCTS

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# Outline

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- Historic Development & Utility of Dissolution Test
- Anatomy of The Eye & Drug Disposition
- Factors That Impact Availability of Topical Ophthalmic Dosage Forms
- Specific Case : Ophthalmic Emulsions
- Summary

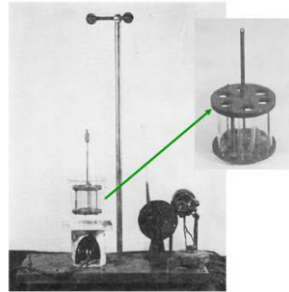
# Historic Development of Dissolution Test



1st tablets manufactured on machines

1897

Switzerland's Pharmacopoeia introduces disintegration test



Stoll-Gersberg disintegration apparatus

1934

1970s

SUPAC-IR

Guidance for Industry

Immediate Release Solid Oral Dosage Forms

Scale-Up and Postapproval Changes: Chemistry, Manufacturing, and Controls, In Vitro Dissolution Testing, and In Vivo Bioequivalence Documentation

1995

1997

Class I

- High Solubility
- High Permeability

Class II

- Low Solubility
- High Permeability

Class III

- High Solubility
- Low Permeability

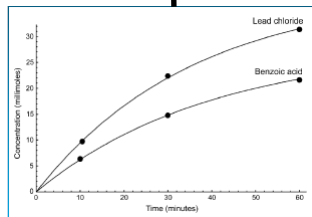
Class IV

- Low Solubility
- Low Permeability

BCS based Bio-waiver

2000

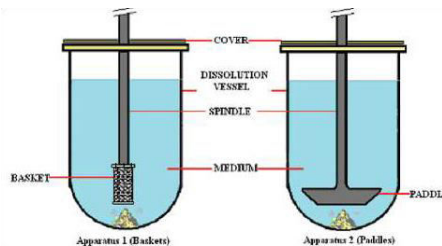
2006



$$\frac{dx}{dt} = C(S-x),$$

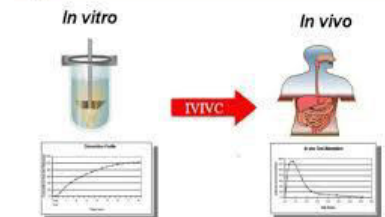
Noyes-Whitney equation

Dissolution test added to USP



FDA Guidance on IR and ER

IVIVC

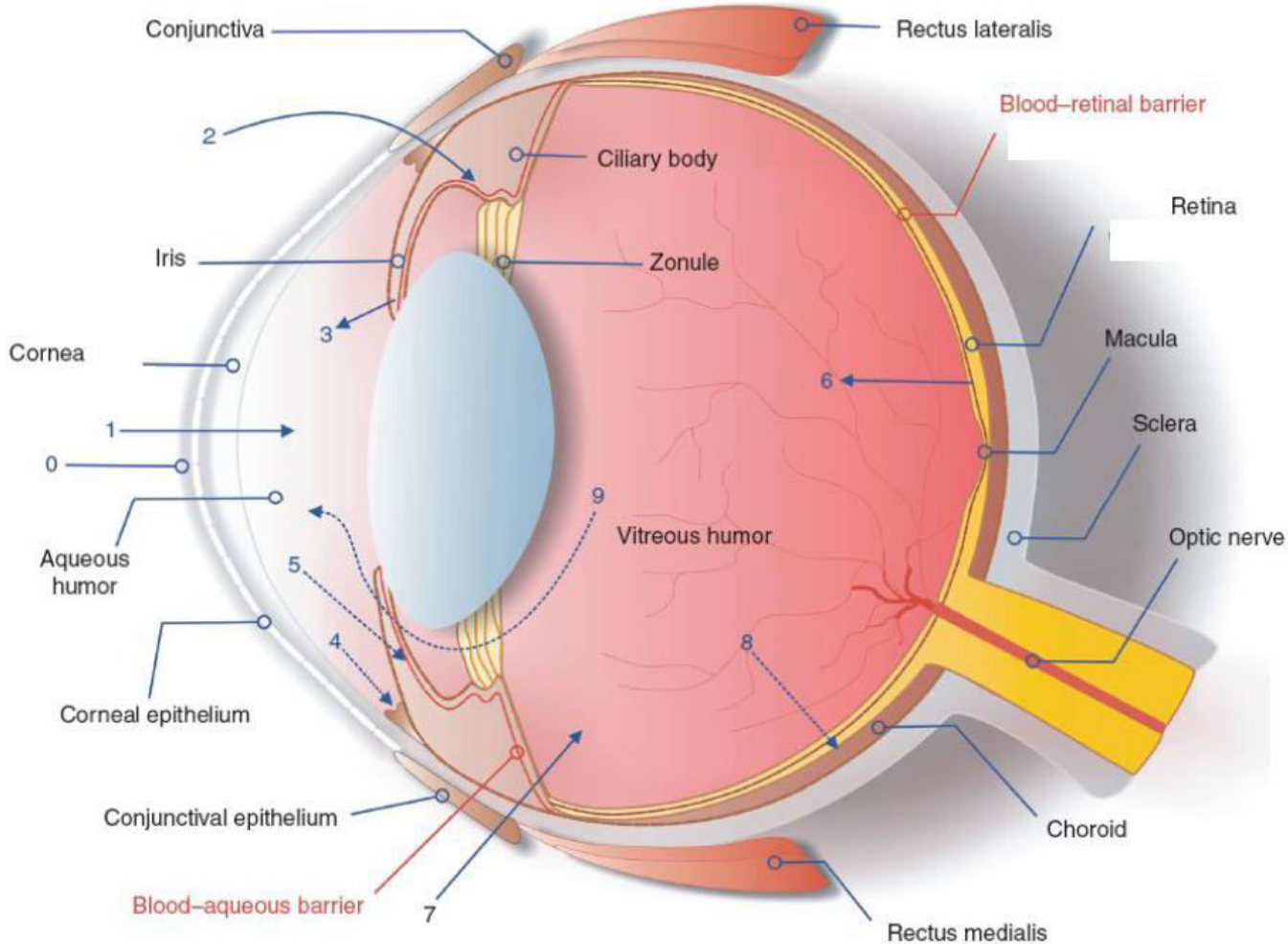


Harmonization between USP, Ph. Eur. and JP

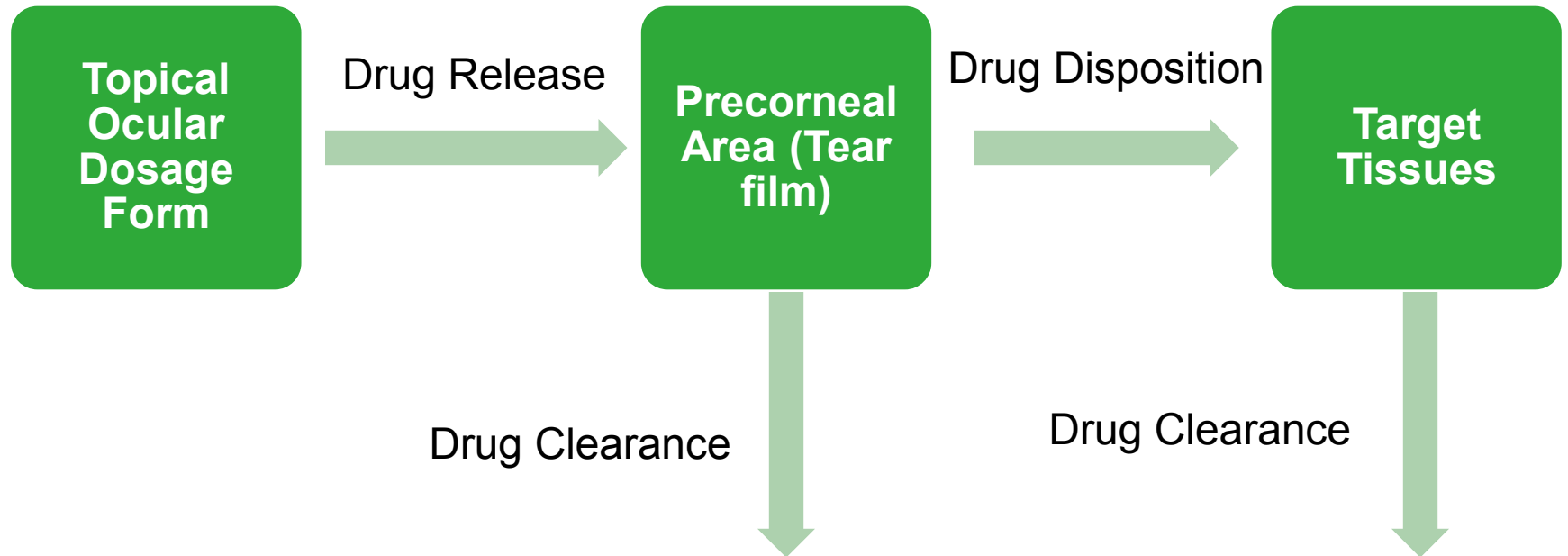
# Utility of Dissolution Testing

- Drug absorption from a solid dosage form after oral administration depends on the release of the drug substance from the drug product, the dissolution or solubilization of the drug under physiological conditions, and the permeability across the gastrointestinal tract.
- Because of the critical nature of the first two of these steps, in vitro dissolution may be relevant to prediction of in vivo performance for some dosage forms
- Based on this general consideration, in vitro dissolution tests for immediate release solid oral dosage forms, such as tablets and capsules, can be used to
  - assess the lot-to-lot quality of a drug product
  - guide development of new formulations
  - ensure continuing product quality and performance after certain changes, such as changes in the formulation, the manufacturing process, the site of manufacture, and the scale-up of the manufacturing process.

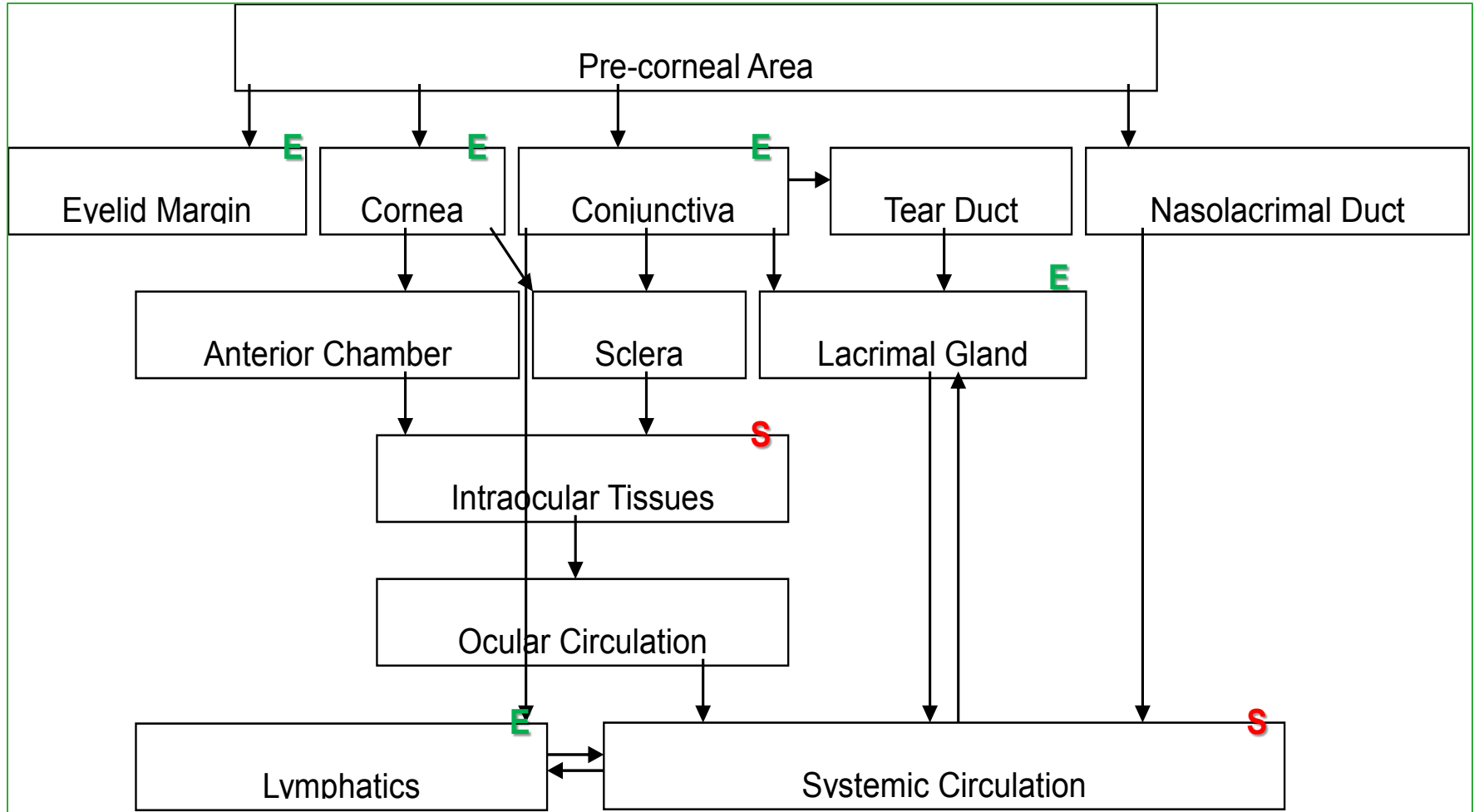
# Anatomy of the Eye



# Performance of a Drug is Reliant on Drug Release and Drug Disposition Kinetics



# Schematic of routes of ocular drug delivery



- Majority of Formulation Cleared thru Nasolacrimal Duct
- Tear Fluid turnover is about every 2 min and most of the delivered formulation is washed out in less time (~ 30 sec)

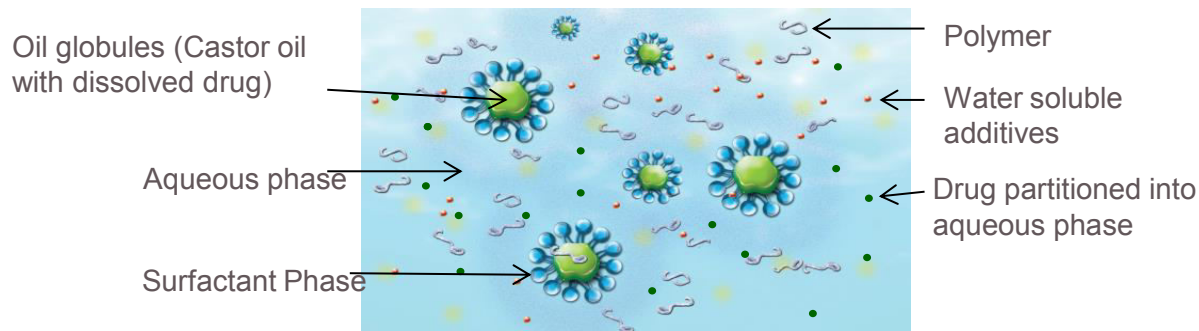
# Some Factors That Can Affect Drug Availability From Topical Ophthalmic Dosage Forms

- Drug Physico-Chemical Properties
  - Molecular Weight, Log P/D, pKa, etc
- Dosage Form Type
  - Solution, Suspension, Emulsion
- Dosage Form Properties
  - Viscosity, pH, Osmolality, Surface tension, Particle size of suspensions, Globule size of emulsions, etc



# Emulsions are Complex Dosage Forms

- Multi-phase systems – contains Oil Phase, Aqueous Phase, Interface consisting of surfactants and other stabilizing polymers, Micellar Structures



- Drug can be distributed in All Phases – oil, aqueous, surfactant and micellar structures
- Amount of Drug in each phase is in dynamic equilibrium and can shift based on external environment (Heat, Shear, Chemical interactions , biological interactions, etc)
- Manufacturing Process is critical to establish:
  - Oil Droplet size
  - Surfactant/Oil Interactions
  - Polymer/Oil/surfactant Interactions
  - Drug Distribution in each of the Phases

Johan Sjoblom, Emulsions and Emulsion Stability, Surfactant Science Series, CRC Press, 2005

# Ophthalmic Emulsions

- Ophthalmic emulsions are complex systems that are used to deliver poorly soluble drugs to the eye, a complex organ with multiple target tissues
- These emulsions are locally acting with negligible systemic levels so PK bioequivalence generally not possible
- Short residence time in the eye (30 sec to 2 min) with complex absorption pathways.
- Manufacturing processes can affect emulsion safety/tolerability and performance by altering drug distribution attributes in the emulsion and hence absorption/distribution kinetics

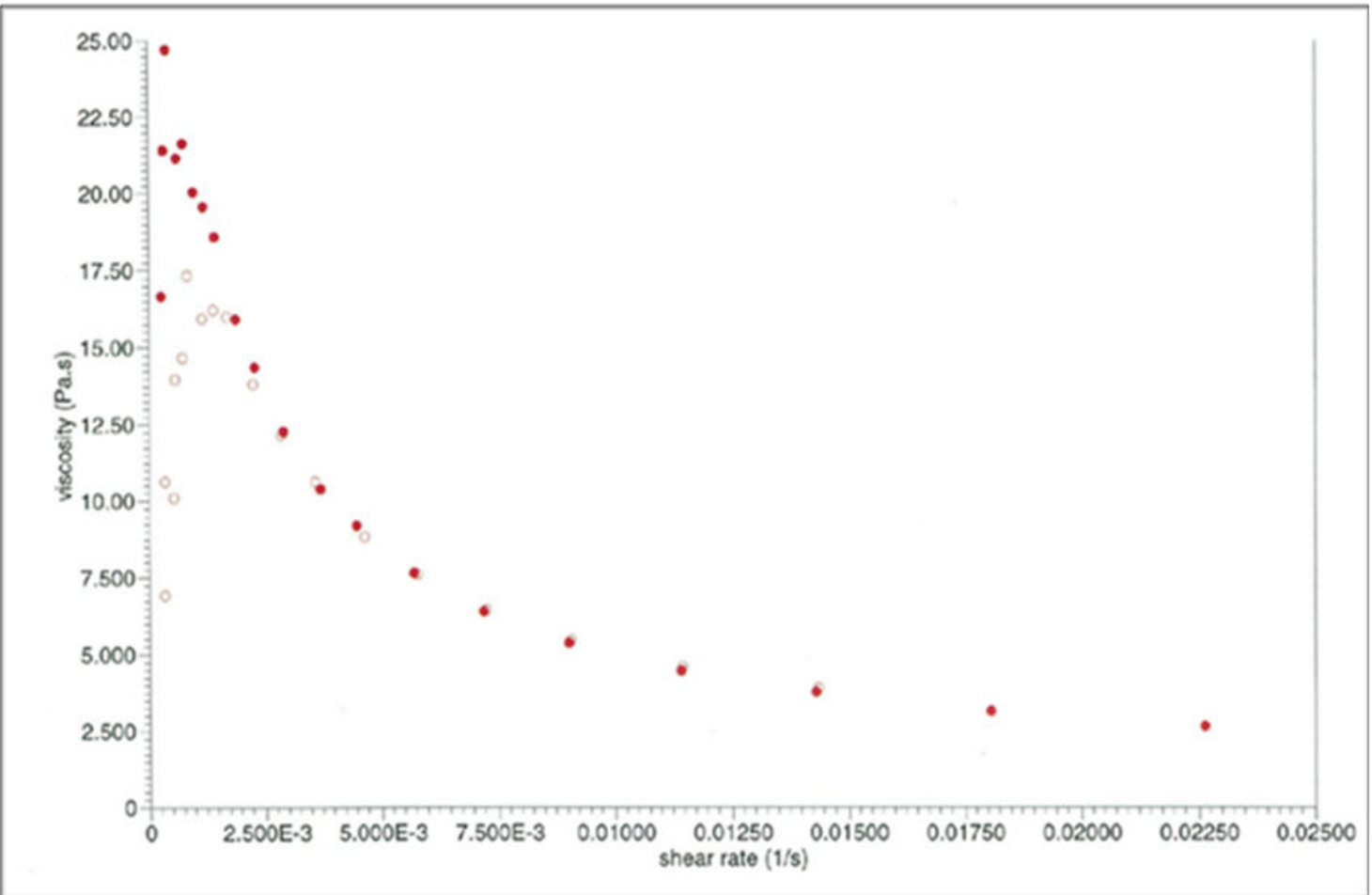
# Impact of Manufacturing Changes on Ophthalmic Emulsion Characteristics and Performance

- Allergan developed a series of different methods to make emulsions similar to RESTASIS® by making selected modifications such as excipient grades, processing times, homogenization methods, sterilization techniques and/or processing temperature. This yielded 9 test emulsions that were Q1/Q2 to RESTASIS®
- Each of these 9 test formulations was compared against RESTASIS® using six physico-chemical properties - globule size, pH, viscosity, zeta potential, surface tension, and osmolality

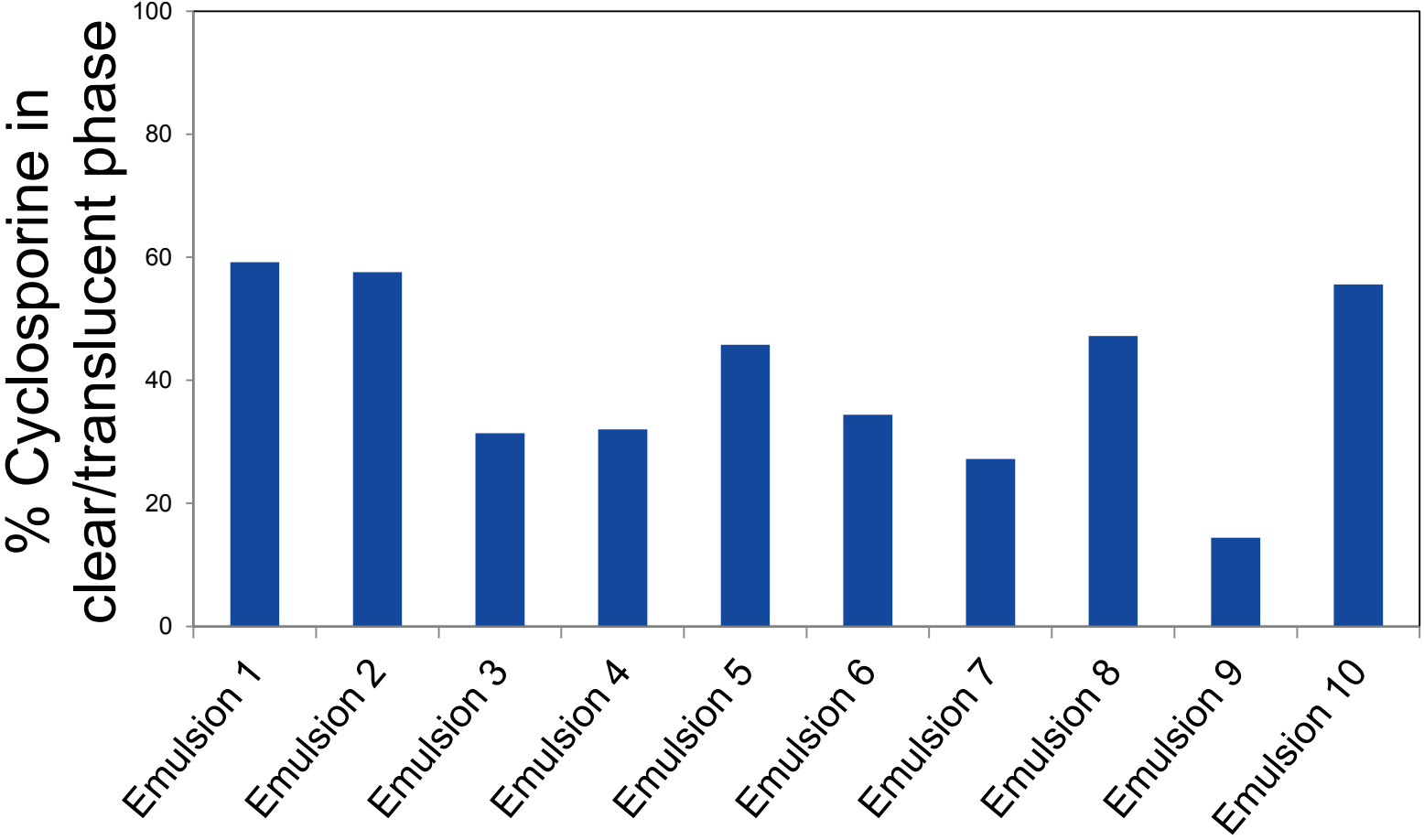
# Impact of Manufacturing Changes on Ophthalmic Emulsion Characteristics and Performance, contd

- Allergan conducted additional testing on these products, which included drug distribution in various emulsion phases, rheology, globule size measurements with a variety of different techniques and the effect of dilution with tears on these physicochemical parameters
  
- Additional assessments were also conducted comparing these test emulsions with RESTASIS<sup>®</sup> to evaluate :
  - In vitro permeability across human corneal epithelial cells
  - In vivo rabbit tear pharmacokinetics and ocular tolerability
  - In vivo dog ocular tissue pharmacokinetics

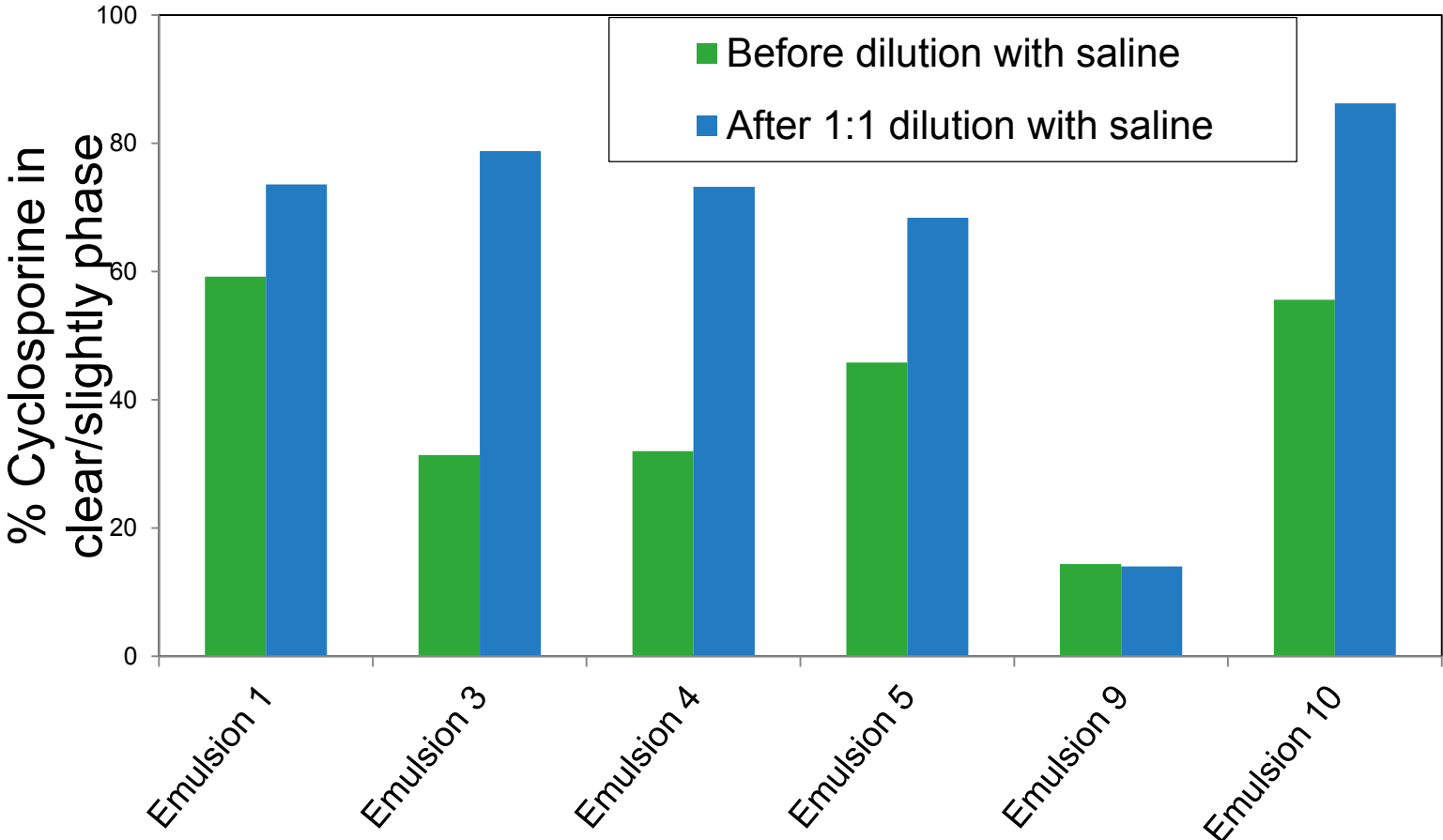
# Rheometry profiles for Q1/Q2 cyclosporine emulsions manufactured using two different techniques



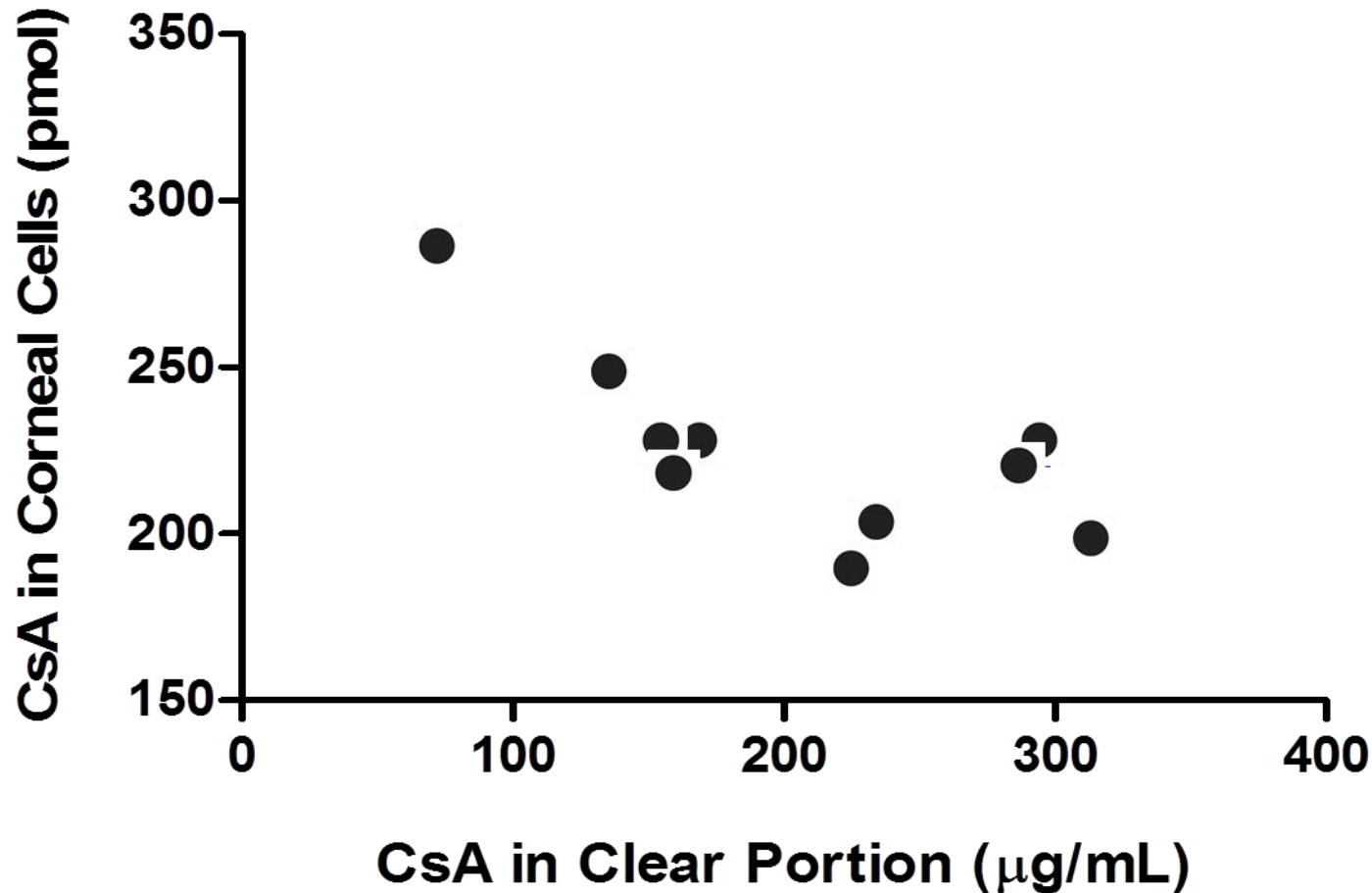
# Percent cyclosporine measured in the clear/translucent phase after centrifugation



# Percent of total concentration of cyclosporine in the clear/translucent phase layer of emulsions before and after dilution with saline solution



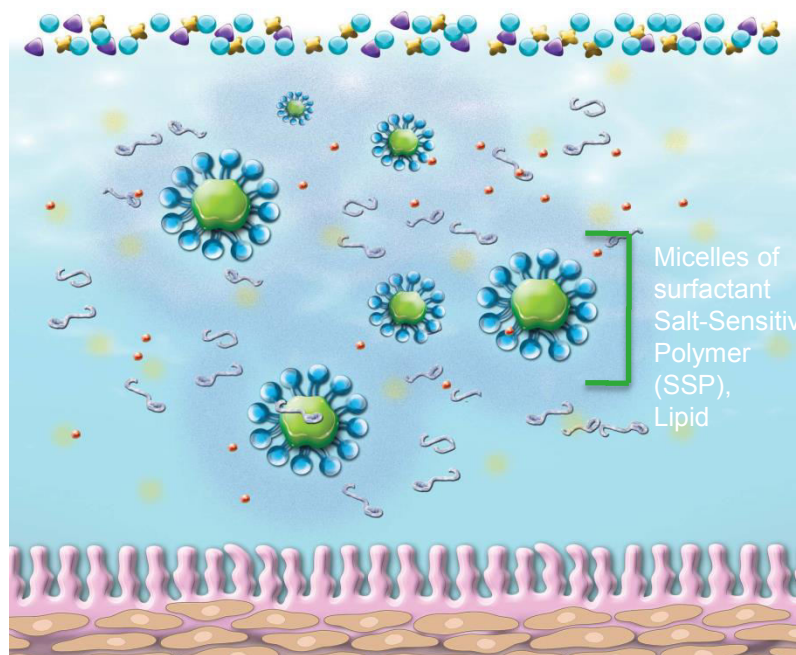
# Effect of amount of cyclosporine measured in the clear/translucent phase of the emulsion on permeability into human corneal epithelial cells





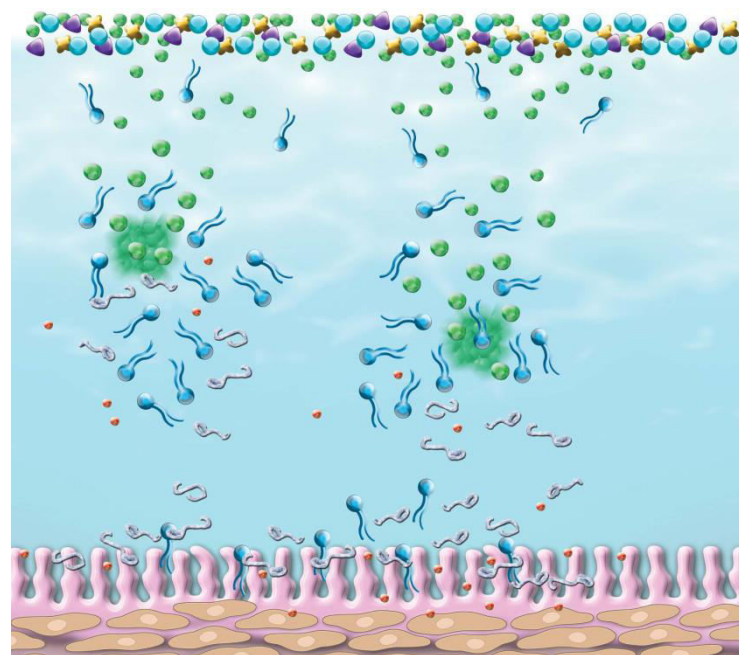
# Tear Film Impacts Emulsion Formulation When Applied Topically to Alter Its Physico-chemical Properties, and Thus Ocular Disposition

## When First Applied to the Eye



- Oil Droplets are stabilized by surfactant and Salt Sensitive Polymer in the container and form complex multiphase micellar structures
- When applied to eye, the components of formulation rapidly mix and interact with Tear Film components

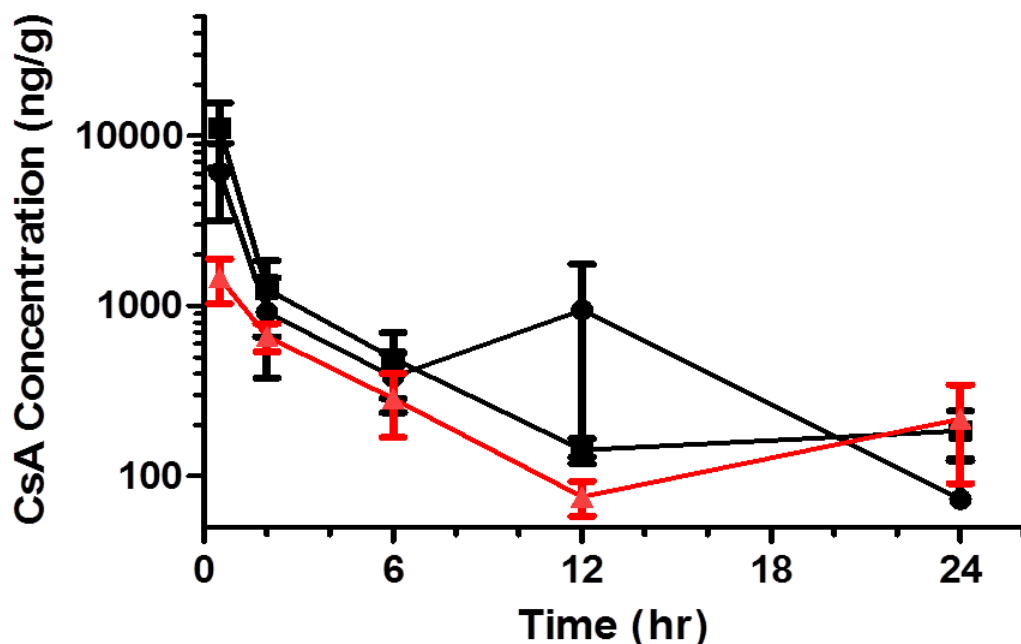
## Rapidly Mixes with Tear Film (within seconds)



- Micelles are destabilized and break apart due to action of salt in the tear film on SSP.
- Lipid released to lipid layer and coalesces to form larger droplets
- Surfactant associates with lipids and mucins in the tear film



# Cyclosporine concentration time profile in rabbit tears following a single 35 $\mu$ L ophthalmic administration of emulsions



Cyclosporine concentration time profile in rabbit tears following a single 35  $\mu$ L ophthalmic administration of emulsions A, B (Black Dots) or **RESTASIS® (Red Triangle)**

Each data point represents a mean value of n=2 to 4 rabbits (4-8 eyes)/timepoint  $\pm$  standard error

# Considerations for Development of “Biorelevant” In Vitro Drug Release Tests for Topical Dosage Forms

- Design for Short duration/residence time available for drug release (< 5 min after application to the eye).
- Mimic tear composition in target patient population and the impact this composition has on the dynamic changes to suspension/emulsion characteristics, such as viscosity changes and emulsion breakup.
- Simulate the impact of (a) tear dilution and (b) turnover rate on drug availability to target tissues.
- Effects of shear from blinking on the emulsion rheology as well as the transport processes.
- Differential drug release and tissue uptake, considering both (a) multiple target tissues expected to be involved in the pharmacodynamic effect, and (b) the fact that for emulsions, tissue uptake can also be through diffusion or direct partitioning from the emulsion phase.

# Summary

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- Drug absorption from a topical ophthalmic dosage form after administration depends on the release of the drug substance from the drug product, the dissolution or solubilization of the drug under physiological conditions, and the permeability across local tissues
- In Vitro release testing can be a useful technique to guide development, Quality assurance purposes, evaluate lot to lot consistency and help determine effect of certain changes such as formulation, scale, manufacturing process & site
- Further understanding of locally acting complex ophthalmic dosage forms such as emulsions is necessary to create scientifically robust In Vitro release methods
- *In vitro* drug release methods that can be linked to *in vivo* performance would be valuable tools for product development, quality assurance and life cycle management of products.

# Allergan Contributors

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- Sesha Neervannan, PhD
- Mayssa Attar, PhD
- Anu Gore, PhD

# Questions / Discussion



# Abstract

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Drug absorption from a dosage form after administration depends on the release of the drug substance from the drug product, the dissolution or solubilization of the drug under physiological conditions, and the permeability across membranes at the site of delivery. While dissolution testing has been utilized as a development and quality control tool for oral dosage forms for several decades, the utility of these tests for ophthalmic dosage forms has not been established yet. An in-depth understanding of ocular physiology and dosage form factors is essential to develop invitro drug release tests for ophthalmic dosage forms. Furthermore, local disposition of the drug and/or formulation determine the performance of ophthalmic dosage forms.

This presentation will focus on the current state of invitro drug release tests for ophthalmic dosage forms. Challenges in determining relationships between in-vitro release and in-vivo performance of locally acting ophthalmic dosage forms will also be discussed.