

ORAL DELIVERY OF MACROMOLECULES



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MOTIVATION

- Oral delivery is one of the most sought after means of drug administration
 1. Its convenience
 2. High patient compliance

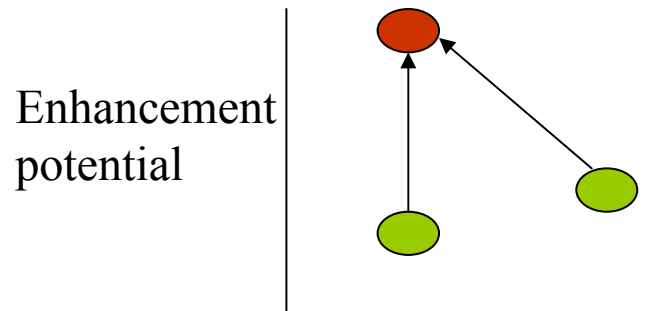
- However it is difficult to administer drugs that are proteins and other macromolecules
 1. Enzyme degradation
 2. Low permeability

PERMEATION ENHANCER

- ❑ An enhancer is a molecule that increases the permeability of intestinal membrane
- ❑ Single permeation enhancers have limited use

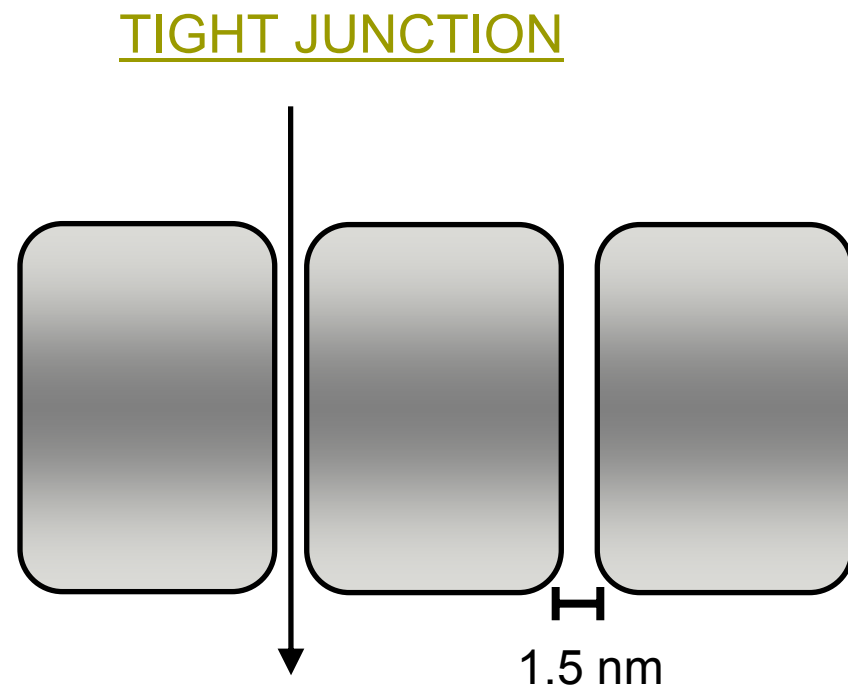
My Goal :

To find synergistic combinations of chemical enhancers

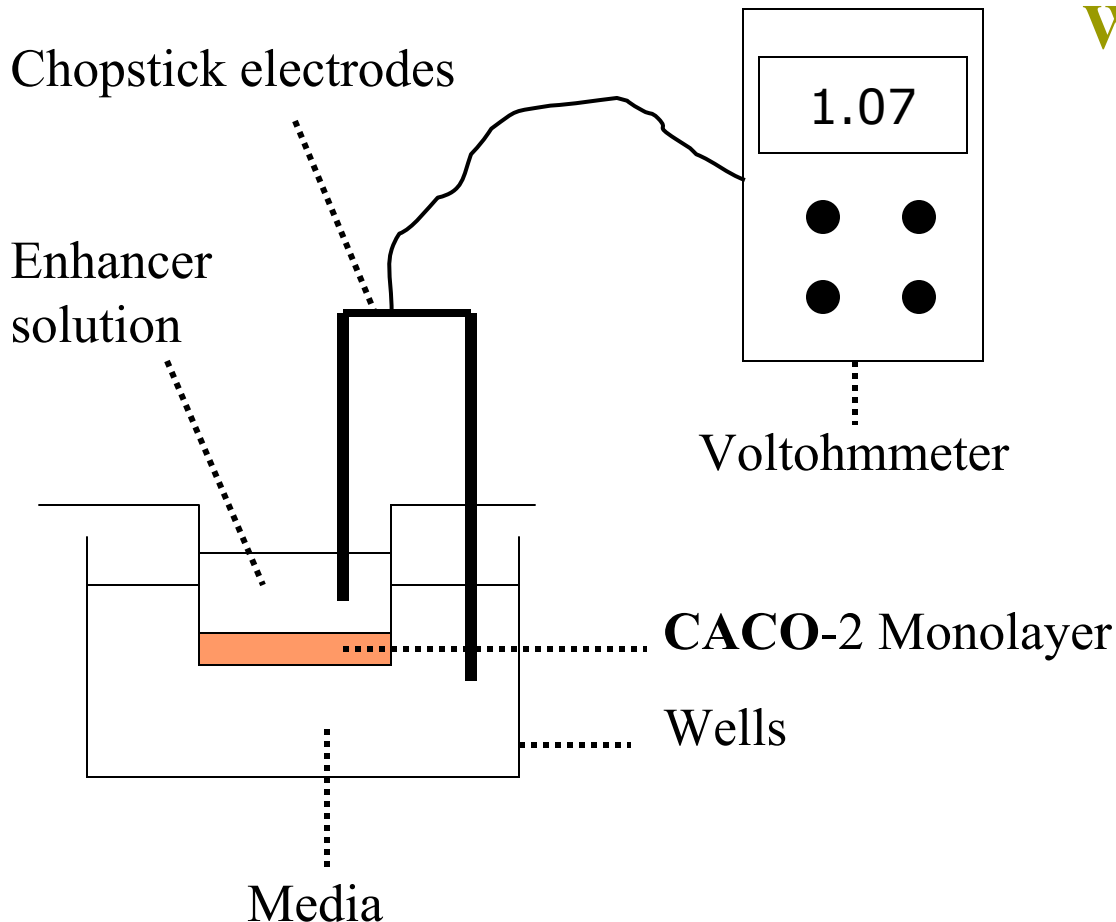


EXPERIMENTAL PROCEDURE

- ❑ Growing and maintaining CACO-2 cells (intestinal cells)
- ❑ 16 different enhancers from 9 distinct chemical categories
- ❑ Exposing cells to the enhancers and then measuring resistance of the cell membrane
- ❑ Enhancers alter the structure of tight junctions



THE VOLTOHMMETER

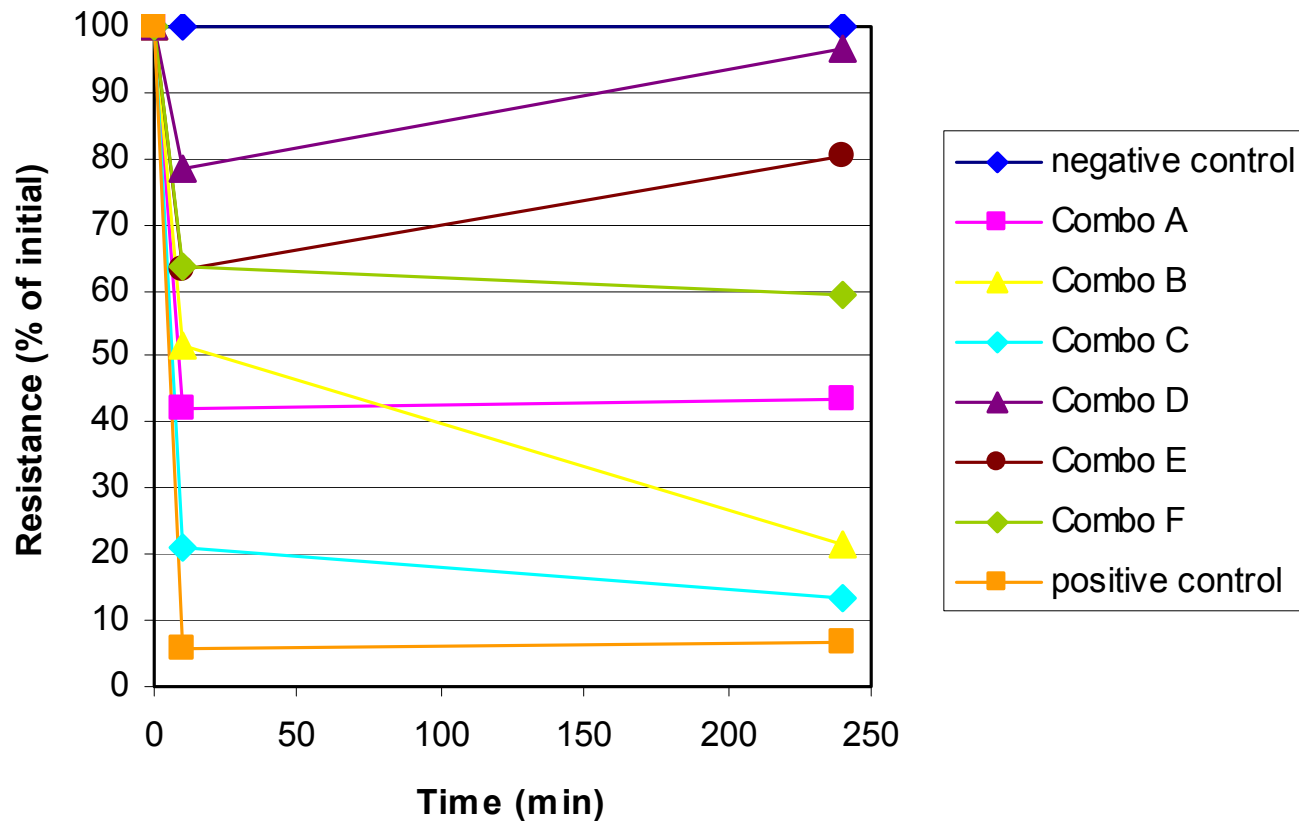


What does it measure?

- It measures the resistance of the Caco-2 Monolayer
- The smaller the resistance, the greater the permeability of the cell membrane

ENHANCEMENT RESULTS

Combination Enhancer Data



ENHANCEMENT AND SYNERGY RESULTS

Combinations		Average Enhancement
SLA	MIE	0.938
SLA	UR	0.935
SLA	TX100	0.934

Combinations		Synergy
DPS	HPA	2.39
UR	EDTA	2.25
HPA	MP	2.09



Anionic Surfactants



Esters



Fatty Amines



Non Ionic Surfactants



Zwitterionic Surfactants



Fatty Acids



Others



Azone-like Molecules

CONCLUSION

- Synergistic combinations of permeation enhancers do exist
 - Interactions between enhancers produce synergy

- Our best enhancers for
 - Potency: SLA and MIE
 - Synergy: DPS and HPA

- Zwitterionic surfactants and fatty esters are more likely to produce synergistic combinations

WHAT'S NEXT?

- Expanding the combination study
 - Testing more combinations from the ideal categories of enhancers

- Performing Safety Analysis of the synergistic combinations
 - Maybe look for synergistic combinations in toxicity

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QUESTIONS ?



COMBINATIONS

Combinations		
A	0.05% UR	0.05% EDTA
B	0.05% UR	0.05% CN
C	0.05% UR	0.05% PPZ
D	0.05% UR	0.05% PO
E	0.05% UR	0.05% MPZ
F	0.05% UR	0.05% Men

EQUATIONS....

ENHANCEMENT POTENTIAL =

$$1 - \frac{\text{TEER}(E) - \text{TEER}(\text{SLS})}{100 - \text{TEER}(\text{SLS})}$$

$$\text{SYNERGY} = \frac{\text{EP}_{X+Y}}{0.5 \text{EP}_X + 0.5 \text{EP}_Y}$$