**INTRODUCTION and OBJECTIVES**

**FUSAFUNGINE**
- Mixture of cyclic hexadepsipeptide enniatins
- Produced by fungi, *i.a.* *Alternaria* and *Fusarium*
- Marketed as oral/nasal sprays, patented in 1953
- Topical treatment of upper respiratory tract infections
- Claimed anti-inflammatory and bacteriostatic effects
- SmPC indicates no systemic absorption

**EXPERIMENTAL**

1. **GC-FID**
   - Five different batches of a fusafungine market preparation
   - Determination of EIOH and IPM concentration

2. **Franz Diffusion Cell (FDC)**
   - Buccal pig mucosa
   - Dose solutions: 1 mg/mL enniatin mix in different EIOH:IPM mixtures
   → $1:9$, $3:97$, $5:95$ and $10:90$ EIOH:IPM (V/V)

3. **UHPLC-MS/MS (MRM)**
   - Analysis of the FDC samples
   - Transmucosal kinetics
   - Steady-state plasma concentrations

**RESULTS and DISCUSSION**

1. **Determination of EIOH and IPM content**
   - EIOH: $1.67 \pm 0.03\%$ (mean ± SEM, n = 5)
   - IPM: $91.60 \pm 2.02\%$ (mean ± SEM, n = 5)
   - No statistical significant difference between batches (p > 0.10)

2. **Transmucosal kinetics**
   - Enniatin able to permeate buccal mucosa!
   - Example enniatin B (most abundant):

   - No statistical significant difference between dose solutions (p > 0.05)
   - Inverse relationship between log $P$ versus $k_{pu}$, $Q_{0m}$ and $Q_{m}$
   - Local mucosa concentrations up to 33 $\mu$M (total enniatins)
   → market preparations x 10 dosage = 330 $\mu$M

3. **Clinical interpretation**
   - Neglecting *in-vivo* saliva flow, GI absorption, metabolism
   - Steady-state plasma concentrations

   $C_{pl,(ass)} = (A \times k_{pu} \times C_{p})/Cl$

   - $Cl$ = plasma clearance
   - $k_{pu}$ = transmucosal permeability coefficient
   - $C_{p}$ = enniatin concentration in vehicle
   - $A$ = exposed mucosal area

   → Ranging from 0.026 mg/L for ENN E to 1.339 mg/L for ENN B
   → x 10 dosage = up to 13.4 mg/L for ENN B alone

**CONCLUSIONS**

- Enniatins in topical medicines are capable of permeating the mucosa barrier!
- $Q_{pu}$ approach → no risk of a significantly different systemic enniatin availability in terms of composition variability.
- Worst-case scenario → question use of enniatins in topical treatment of innocent upper respiratory tract infections → long-term chronic effects?

**REFERENCES**

