

**TRANSDERMALS:  
DERMACEUTICALS, OTC's  
& COSMECEUTICALS**

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# DECADES OF LEARNING

# PRE - HISTORY

- 19TH CENTURY: MERCURY -  
SYPHILIS
- 1960's: NITROGLYCERIN  
SEMI - SOLID
- 1970's to 2007: ALZA  
(ALEX ZAFFARONI)

# HISTORY

- 1968: CONVENTIONAL WISDOM – NOT PRACTICAL
- *IN VIVO* HUMAN DATA SUGGEST CONTRARY
- 1969 & 1974: J INVEST DERM

# **HUMAN *IN VIVO* DATA**

- 1. TESTOSTERONE**
- 2. PROGESTERONE**
- 3. ETHINYL ESTRADIOL**

# CLINICAL ACCEPTANCE

- SLOW
- MILLIONS \$ – SCOPOLAMINE
- TODAY – BILLIONS &  
GROWING

**FDA ROLE: 505 b2**

# GENERATION 1

- SCOPOLAMINE
- CLONIDINE
- NGT
- NICOTINE

# GENERATION 2

- SELEGILINE
- METHYLPHENIDATE
- GENERICS

# GENERATION 3

- NCE's

# VITRO vs. VIVO FLUX

- DOABLE (ALZA)
- BUT NOT ALWAYS EASY!
- FAILURES– NOT PUBLISHED
- “DEVIL IN DETAILS”
- KNOW HOW !

# **ORAL DOSE FEASIBILITY**

**~ 10 MG OR LESS**

# **FINANCIAL CONSIDERATION**

**MONTELUKAST (SINGULAR)**

**\$2+ BILLION**

**VS**

**GLYBURIDE**

**\$200 MILLION**

# CURRENT TRANSDERMAL

- POTENT
- SMALL < 500 MW
- Log P NARROW RANGE

# ROUTES OF EXPOSURE

- ESTHER STUDY

ORAL ESTROGEN BUT

NOT TRANSDERMAL:

↑ VENOUS THROMBOSIS

(CIRCULATION, 115: 840)

# EARLY EXPLORATION

- SKIN vs ORAL METABOLISM
- PEAK vs FLAT BLOOD LEVEL  
(SLOW RELEASE)

# **DRUG LOAD (MG)**

**0.015 NORELGESTROMINE**



**80.0 METHYLPHENIDATE**

# **WEAR TIME**

**1.0 → 7 DAYS**

# DRUG AREA (cm<sup>2</sup>)

10 – ESTRADIOL



40 – SELEGILINE

# NSAID's

DRUG    pKa    PC    log Kp    Jmax

(HADGRAFT: INT J PHARM, 207: 311)

# NSAID's

DRUG                      FLUX                      IC 50 (COX-2)

(CORDERO 2001)

OTHER PARAMETERS MUST  
BE BALANCED !

# ENHANCERS

PERCUTANEOUS  
PENETRATION ENHANCERS

SMITH & MAIBACH (2ND EDITION)

HIGH THROUGHPUT SCREENING  
S.M.

# **TRANSDERMALS: TEN STEPS**

CLEARANCE FROM DERMIS  
(ID INJECTION)

MODELS: NA SALICYLATE  
CALCEIN NA  
FITC – DEXTRANS

# TRANSDERMALS: TEN STEPS– *con't.*

- DIFFUSION COEFFICIENTS DETERMINED
- DECREASED WITH  
↑ MOL. WT.
- \*MUSCLE RESERVOIR

(YOSHIDA: EUR J PHARMAC SCI, 35:5)

# TRANSDERMAL

- 12 TRANSDERMAL PATCHES
- INTERINDIVIDUAL VARIATION
  - CV OF  $C_{max}$
- INVERSELY CORRELATED
  - MOL. WT.
  - LIPOPHILICITY

# TRANSDERMAL– *con't.*

- MAXIMAL FLUX
  - HB ACCEPTABILITY

(FARAHMAND: INT J PHARM SCI)

# DERMAL

CV: NICOTINE – 26%

NITROGLYCERIN – 53%

# ORAL

CLONODINE – 12%

TESTOSTERONE – 202%

(FARAHMAND: INT J PHARM SCI)

# IRRITATION

## 1) FLUX

- THE ACTIVES
- ENHANCERS

(KAWAHARA: PHARM RES, 24:399)

## 2) ANTI IRRITANTS

(CHEW & MAIBACH: IRRITANT DERMATITIS, p. 421)

# **SPECIAL POPULATIONS**

- **ELDERLY**
- **INFANTS &  
YOUNG CHILDREN**

**ADHESION**

**A FRONTIER**

**AWAITING MASTERY**

# PATCHES

## REMOVING BLACKISH ADHERENT MATERIALS

- MICROPORE<sup>®</sup> (ACRYLATE)
- SOAP & WATER: NOT EFFICIENT
- SIMILAR MATERIAL ON WINDOW PANE
- ACETONE (& ETHER): EFFICIENT

(SEKAR & SRINIVAS: IND J DERM, 74: 397)

# **ALLERGIC CONTACT DERMATITIS**

- **FDA GUIDELINE ?**
- **BIOLOGY – TECHNOLOGY**
- **DOUBLE HRIPT**
- **CLINICAL RELEVANCE IS  
KEY !!**

# **PATCH vs SEMI SOLID**

- **TESTOSTERONE**
- **DICLOFENAC**

**THE “RULE” IS  
PASSIVE DIFFUSION  
IS ACTIVE TRANSPORT  
PRACTICAL ?**

- **FLURBIPROFEN**

(ITO: J CONT RES, 2007)

# **NEW SYSTEM**

- **IONTOPHORESIS**
- **MICRONEEDLES**
- **THERMAL**
- **NEEDLE FREE JET INJECTORS**
- **ETC.**

# **SEX + RACIAL DIFFERENCES IN PHARMACOLOGIC RESPONSE**

- **EFFECT OF ADMINISTRATION  
ROUTE**
- AND**
- **DRUG DELIVERY SYSTEM ON  
PHARMACOKINETICS**

**(J WOMEN'S HEALTH, 14:30)**

# **GENERIC**

## **1ST GENERATION LESSON**

- **DILIGENCE !**
- **ADVANCING KNOWLEDGE**
- **MORE COMPLEX THAN APPRECIATED**
- **HENCE – FAILURES**

# CRYSTALLISATION

- SCOPALAMINE
- ROTIGOTINE
- ETC.

BASIC CHEMISTRY CHALLENGE

# **BARRIER TO SUCCESS**

**C. CHRISTENSON**

**INNOVATORS DILEMMA**

# CONCLUSION

- NOT SO SIMPLE !!
- REQUIRES  
TEAM COOPERATION

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