I V P T

IN VITRO

PERMEATION TEST

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KEY BIOLOGIC | PHARMACOLOGIC QUESTIONS

1) IVPT VALUE FOR BIOEQUIVALENCE ?

2) IVPT – COMPARED TO IN VIVO?
   - DOES IT MATTER?

“THE BEGINNING”

GEORGE BURCH

TULANE MEDICAL SCHOOL

INTERNAL MEDICINE

PHYSIOLOGY – TEWL

BEGINNING – CHEMICAL WARFARE

IVPT – WORLD WAR II – UNITED KINGDOM

R. TREGEAR: PHYSICAL FUNCTIONS OF SKIN, ACADEMIC PRESS, 1966

OLD AND NEW TESTAMENT COMBINED.

BIBLIOGRAPHY

SCHAEFER

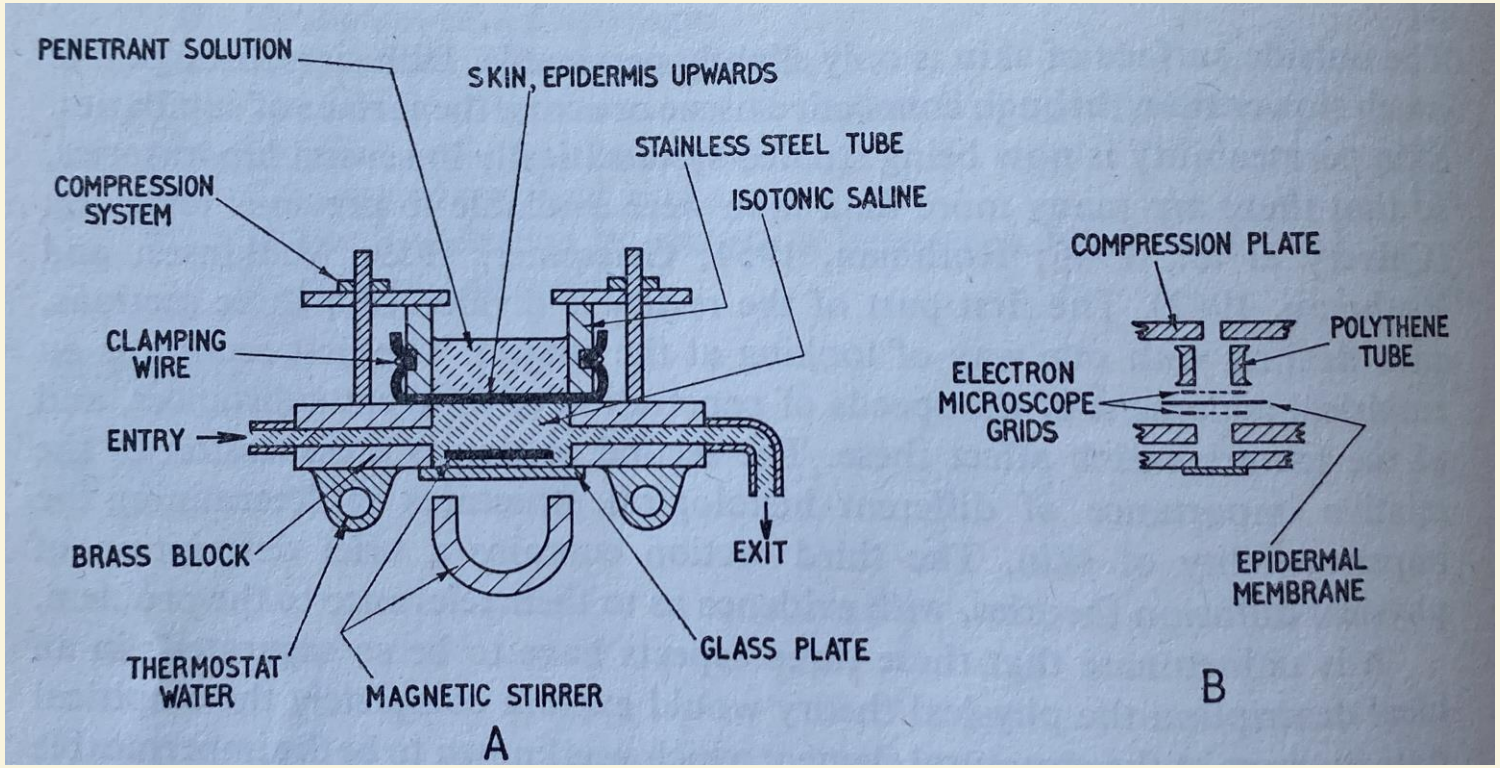
- HANDBUCH DER HAUT BOOK 14B 1981

  40 PAGES – REFERENCES

- SKIN BARRIER– KARGER, 1996

FIRST CHAMBERS

TRAGEAR



Diffusion cells, as used for the measurement of penetration by isotope-labelled chemicals though (A) skin or (B) epidermal membranes.

FLOW THROUGH SYSTEMS

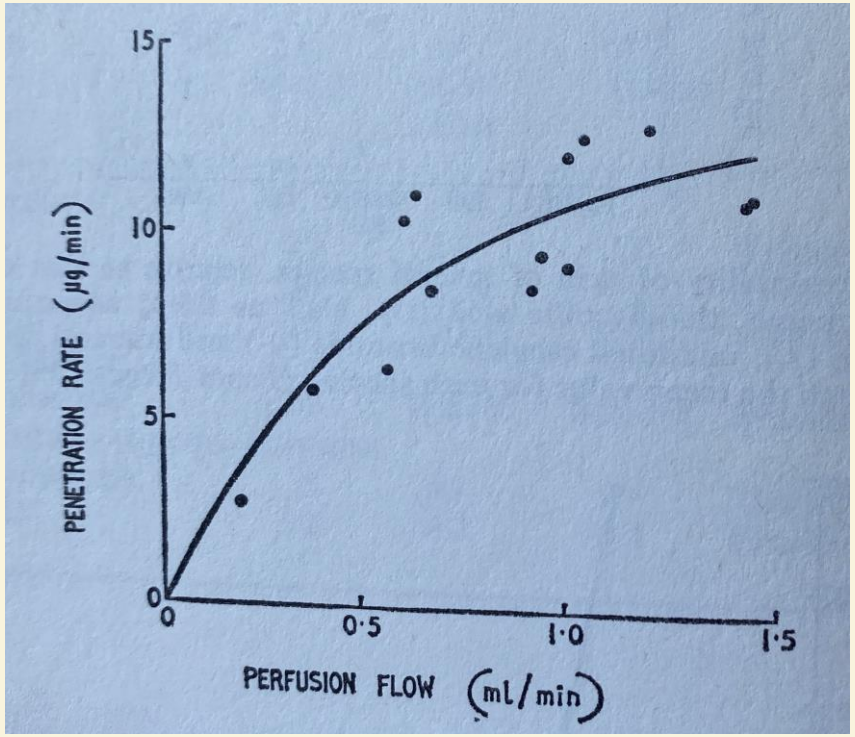
ANSWORTH: J SOC COS CHEM, 11:69, 1960

MARZULLI: J INVEST DERM, 39: 387, 1962

BRONAUGH: IN VITRO ABSORPTION, CRC PRESS, 1991

FLOW THROUGH CELL: PERFUSION RATE

TREGEAR



The penetration of tri-n-butyl phosphate through perfused pig skin, related to the perfusion rate. The results from eight experiments are included.

FLOW THROUGH RATE: VS. STATIC

Wm. CRUTCHER: J INVEST DERM, 53: 264, 1969

- LIMITED DATA | POWER
- LIMITED FLOW RANGES | SOLUBILITIES

SKIN SURROGATES

- MEMBRANES
  - NUEPANE PHARMACEUTICS, 12:152, 2020
- HUMAN SKIN EQUIVALENTS (HSE)
  - BOUWSTRA ADVANCED DRUG DELIVERY REV, 2021

CELL DESIGN

STEPHEN FRANTZ

[B. KEMPPAINEN: METHODS FOR SKIN ABSORPTION, CRC PRESS, 2000]

METRICS – SKIN ‘NORMALITY’

- BRONAUGH — TRITIATED WATER
- NANGIA — TEWL (TRANSEPIDERMAL WATER LOSS), INT J PHARM, 170: 33, 1998
- ELECTRICAL PROPERTIES: INPEDENCE | CAPACITANCE

MASS BALANCE
SKIN COMPARTMENTS

- SURFACE RESIDUE (NOT ABSORBED)
- STRATUM CORNEUM TAPE STRIPPING (PERFECT NUMBER?)
- STRATUM CORNEUM
- EPIDERMIS
  - DERMIS
  - RESERVIOR

IDEAL: > 95% APPLIED DOSE

[BUCKS: J INVEST DERM, 90:29, 1988]

SEPARATING SKIN LAYERS

- STRATUM CORNEUM
- EPIDERMIS
- DERMIS

[ZOU: ARCH DERMATOL RES, 310:1, 2018]

REGIONAL VARIATION

NORMALIZE TO OTHER SITES

[GUY: IN BRONAUGH'S PERCUTANEOUS ABSORPTION, 2ND ED., Page 461]

METABOLISM

KAO, JOHN: 'COLD' CHEMISTRY vs. 'RADIOLABELS'

KEMPPAINEN, B: METHODS FOR SKIN ABSORPTION, CRC PRESS, 1990 PAGE 192

METABOLISM

FRESH vs. FROZEN SKIN

- VIABILITY ASSAYS (GLUCOSE)
- TISSUE CULTURE IN RESERVOIR
- MAN vs PIG !
- CHEMICAL SPECIFICITY ?

VITRO vs VIVO

MAN ?

AGREEMENT – WITH – IN VIVO HUMAN DATA

- VITRO | VIVO RATIO (ALL DATA) 0.18 TO 19.7
- VITRO | VIVO RATIO (HARMONIZED) 0.58 TO 1.28

AWAITS REPLICATION

[LEHMAN: SKIN PHARMACOL PHYSIOL, 24:224, 2011]

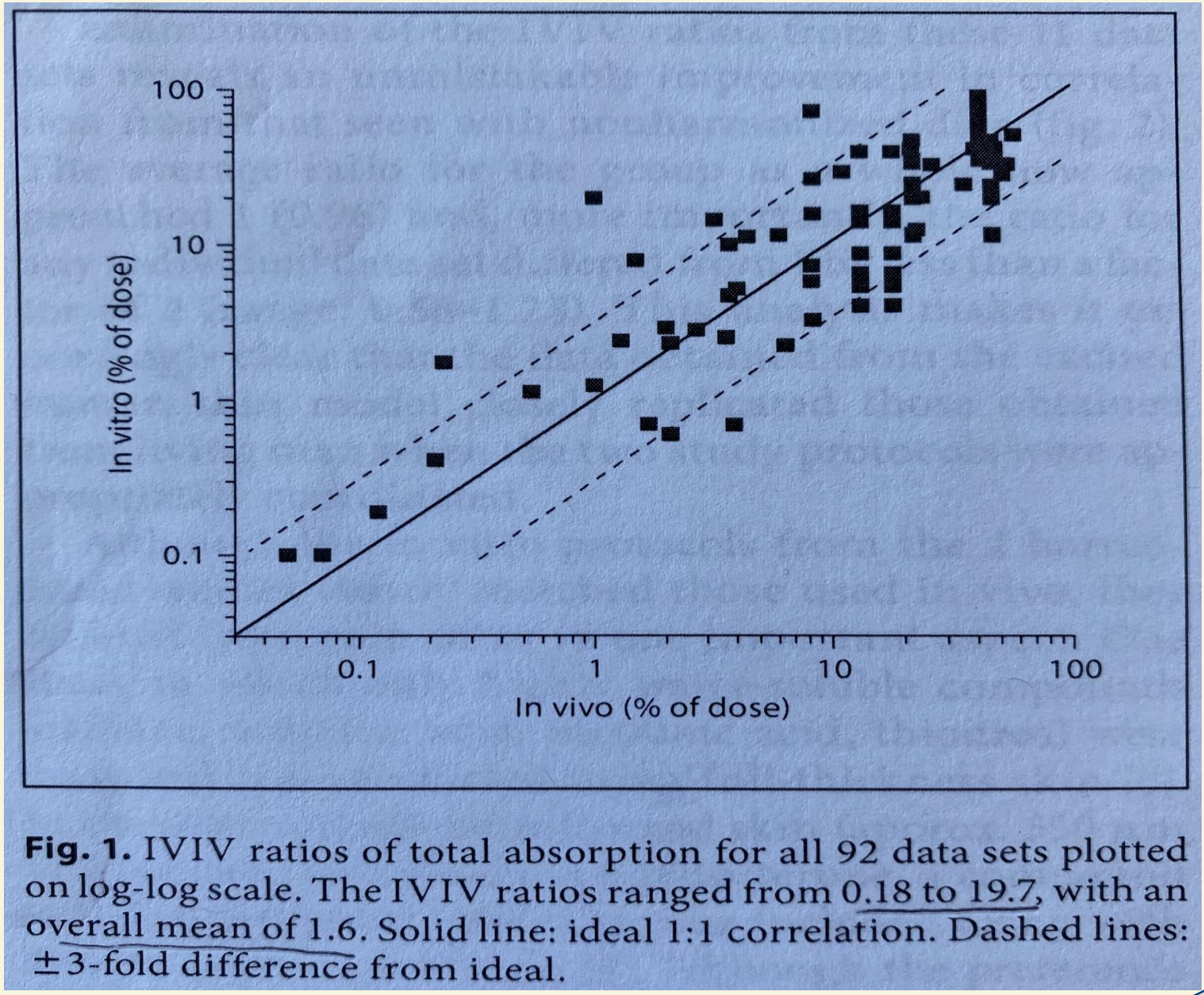


Fig. 1. IVIV ratios of total absorption for all 92 data sets plotted on log-log scale. The IVIV ratios ranged from 0.18 to 19.7, with an overall mean of 1.6. Solid line: ideal 1:1 correlation. Dashed lines: ±3-fold difference from ideal.

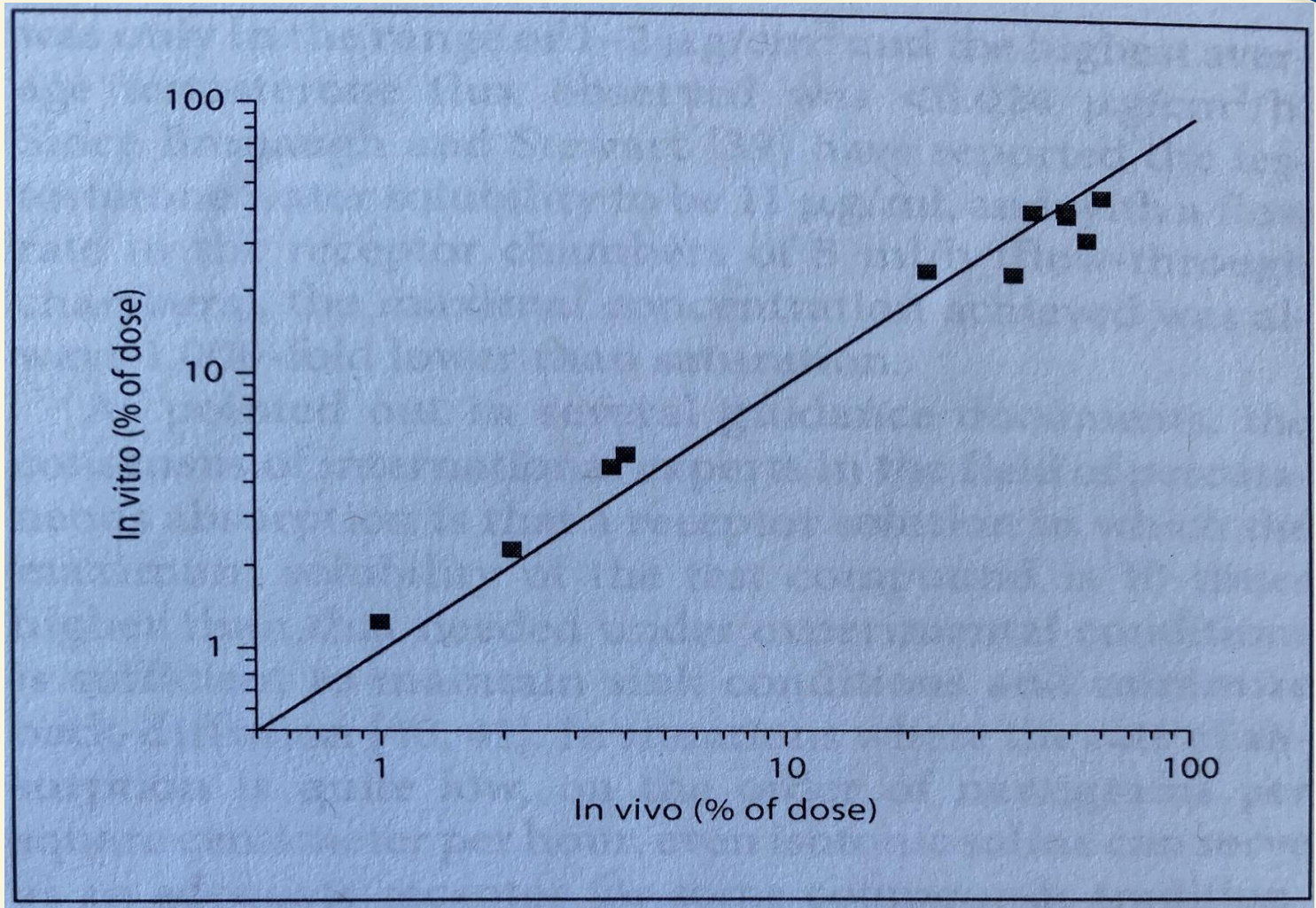


Fig. 2. IVIV ratios of total absorption for 11 fully harmonized data sets plotted on log-log scale. The IVIV ratios ranged from 0.58 to 1.28, with an overall mean of 0.96. Line: ideal 1:1 correlation.

PROTEIN BINDING

STRATUM CORNEUM– SUBSTANTIVITY

EPIDERMIS

DERMIS

FAT– ?

[MENCZEL J INVEST DERM, 54: 386, 1970]
[HUI J APPLIED TOX, 33:157, 2013]

IN VIVO COMPLEXITY
20+ STEPS !

LAW: AM J CLIN DERMATOL, 2020 FEB; 21(1): 85-9

1	RELEVANT PHYSICO-CHEMICAL PROPERTIES (PARTICLE–SIZE | MOLECULAR WEIGHT, LIPOPHILICYT, PH, Pk_a, PARTITION COEFFICIENT
2	VEHICLE | FORMULATION
3	CONDITIONS OF DRUG EXPOSURE (DOSE, DURATION, SURFACE AREA, EXPOSURE FREQUENCY
4	SKIN APPENDAGES (HAIR FOLLICLES, GLANDS) AS SUB-ANATOMICAL PATHWAYS
5	SKIN APPLICATION SITES (REGIONAL VARIATION IN PENETRATION

6	POPULATION VARIABILITY (PREMATURITY, INFANTS, AGED
7	SKIN SURFACE CONDITIONS (HYDRATION, TEMPERATURE, PH
8	SKIN HEALTH AND INTEGRITY (TRAUMA, SKIN DISEASES)
9	SUBSTANTIVITY AND DBINDING TO DIFFERENT SKIN COMPONENTS
10	SYSTEMIC DISTRIBUTION AND SYSTEMIC TOXICITY
11	EXFOLIATION
12	WASHING-OFF AND WASHING - IN
13	RUBBING | MASSAGING
14	TRANSFER TO OTHERS (FROM HUMAN TO HUMAN AND HARD SURFACE TO HUMAN)

15	VOLATILITY
16	METABOLIC BIOTRANSFORMATION | CUTANEOUS METABOLISM
17	PHOTOCHEMICAL TRANSFORMATION | AND PHOTOSENSITIVITY
18	EXCRETION PHARMACOKINETICS
19	LATERAL SPREAD
20	CHEMICAL METHOD OF DETERMINING PERCUTANEOUS ABSORPTION

CLINICAL RELEVANCE
DISEASE | DAMAGED SKIN

- GATTU: SKIN PHARM PHYS 23: 171, 2010
- GATTU: SKIN PHARM PHYS 24: 2, 2011 APPROXIMATING 2 FOLDS
- BARRIERS – ALL SKIN COMPARTMENTS

IN VIVO HUMAN DATA BASES

OPPORTUNITIES

FOR *IN VITRO* 'VALIDATION'

- CORTICOSTEROID VASOCONSTRICTION
  - RB STOUGHTON
- TRANSDERMALS
  - S. FARAHMAND, INT'L J PHARMACEUTICS, (2009), 367 (1-2), pp 1-15

GUIDANCES

- GROUP “DISCUSSIONS”| JUDGEMENTS
  - O E C D
  - E P A

- DATA WILL BE FINAL ARBITER !

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