Mechanistic Understanding of Subject-by-Formulation Interactions

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Outline

- **Mechanistic Definition**
- **General Paradigm**
- **Case Study**
- **Analysis**
- **Conclusions**

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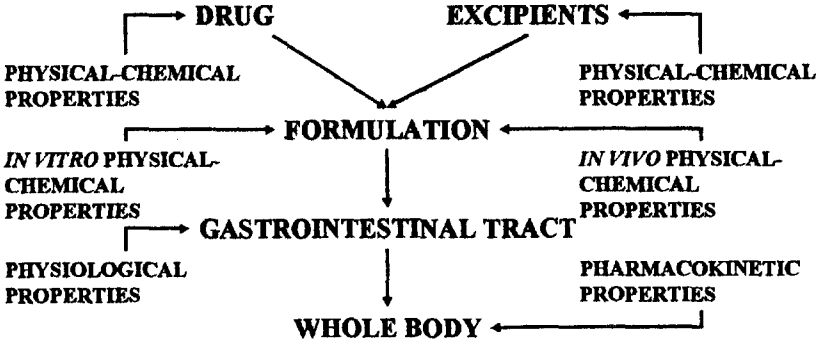
Mechanistic Definition of SxF

- **When the *in vivo* dissolution of a formulation, and absorption of its drug, display sensitivity to physiological variables in the GIT *within the range* found in healthy and/or patient volunteers, and/or**
- **When the excipients in a formulation influence physiological variables, or the physical-chemical properties of a formulation and/or its drug, in the GIT**

General Paradigm



Risk Factors: Drug Properties

- SxF Unlikely
  - HS/HP (BCS I Class)
  - rapid intrinsic dissolution
  - site- and transit time-independent absorption
  - no physical or chemical incompatibilities
  - achiral
  - uncomplicated PK
  - no regional pharmacological effects
- SxF Likely
  - LS/LP (IV), LS/HP (II) and HS/LP (III)
  - slow intrinsic dissolution
  - site- and transit time-dependent absorption
  - physical or chemical incompatibilities
  - complicated PK
  - pharmacological effects on GIT

Risk Factors: Excipient Properties

- Unlikely
  - no effects on GIT pH
  - no effects on permeability
  - no effects on transit time
  - no physical or chemical interactions
  - no effects on presystemic CYP 3A4 metabolism
  - no effects on PGP and other transport processes
- Likely
  - alters local GIT pH
  - promotes permeability
  - pharmacological effect on GIT motility
  - physical or chemical interactions
  - inhibits presystemic CYP 3A4 metabolism
  - reduces PGP and other efflux systems

Risk Factors: Formulation Properties

- **Unlikely**
  - pharmaceutical equivalents
  - simple formulations
    - solutions
    - solid, oral IR
  - low excipient/drug ratio
  - uncomplicated manufacturing
  - rapid and pH-independent dissolution
- **Likely**
  - not pharmaceutical equivalent
  - complex formulations
    - transdermal
    - MR
  - high excipient/drug ratio
  - complicated manufacturing
  - slow and pH-dependent dissolution

Risk Factors: GIT Properties of Subjects

- **Physiological Variables**
  - pH gradient
  - gastric emptying time
  - SITT
  - colonic residence time
  - intestinal permeability gradient
  - activity and capacity of enterocyte CYP 3A4
  - activity and capacity of intestinal transport processes
- **Physiological Range**
  - genetic or environmental control
  - gender
  - age
  - race
  - disease states
  - diet
  - co-administered drugs

Case Method Approach

- **Stepwise analysis of actual examples of SxF**
  - **determine risk factors of drug, excipients, formulation and subjects**
  - **obtain insight into mechanism**
- **When multiple risk factors are present at the same time, a SxF is most likely to occur**

CASE STUDY:

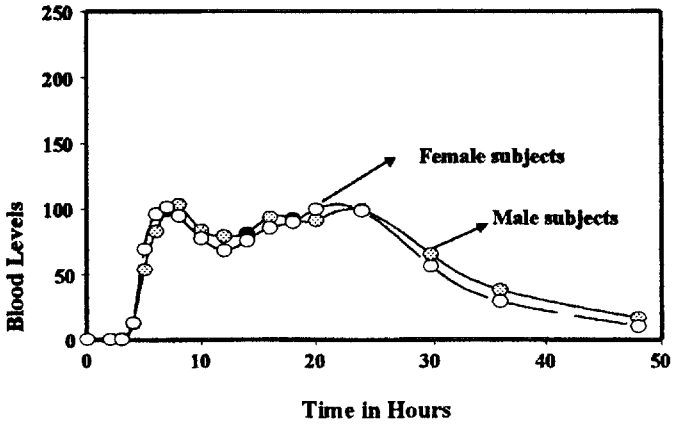
CALCIUM-CHANNEL BLOCKER

(DRUG X)

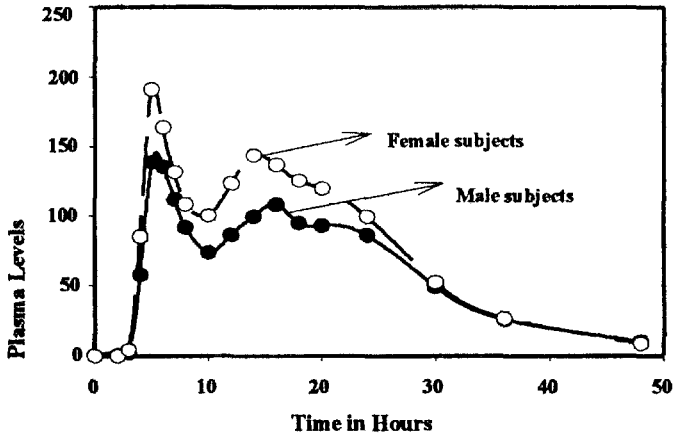
Clinical Study Summary

- **Two-way crossover, non-replicated, single dose, fasting BE study**
- **Healthy, young males (n = 12) and females (n = 13)**
- **Oral capsules**
- **Plasma levels of parent (P) and metabolite (M)**
- **Standard ANOVA analysis of [S(G) x F]**

PK Data for Parent: Product A



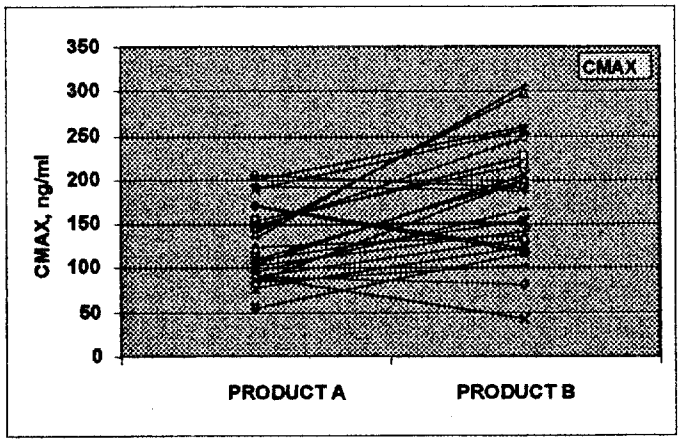
PK Data for Parent: Product B



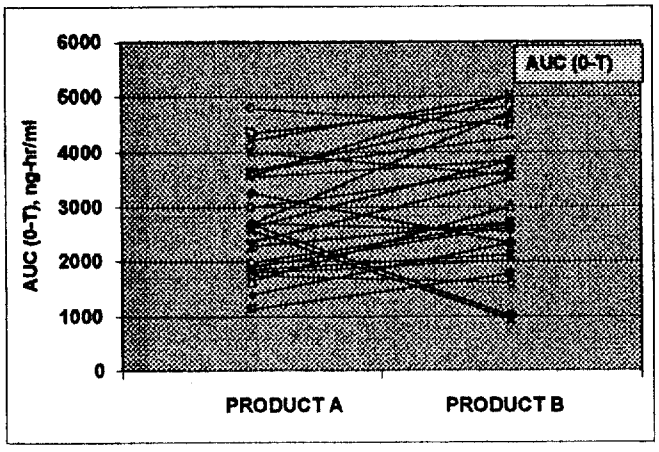
BE Data

	Mean Cmax (%CV)	Mean AUC (%CV)
Males		
Product A	129 ng/ml	3102 ngxhr/ml
Product B	147	2953
Overall % CV	32.1	34.5
A/B Ratio	0.92	1.11
Females		
Product A	129 ng/ml	2785 ngxhr/ml
Product B	201	3549
Overall % CV	19.8	14.4
A/B Ratio	0.62	0.77

Stick Plot: All Subjects



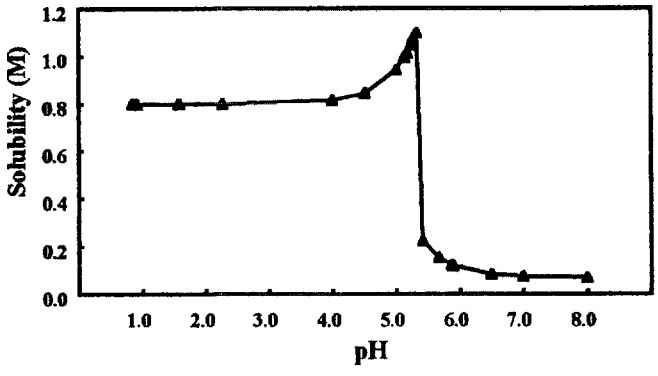
Stick Plot: All Subjects



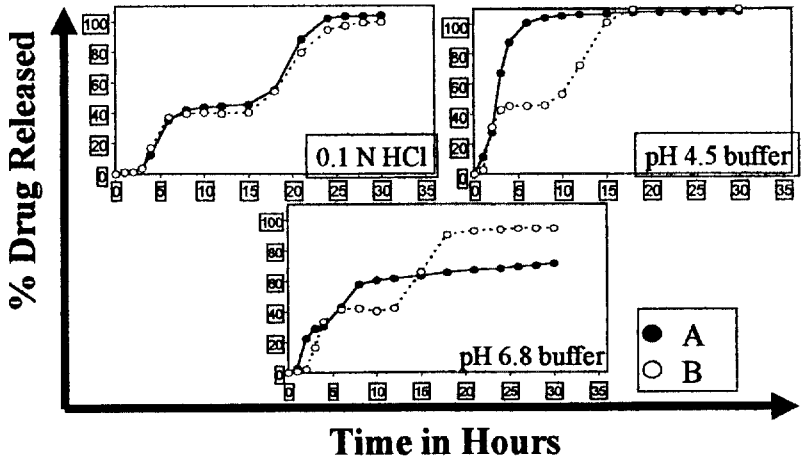
Step-Wise Analysis

- **Risk Factors**
  - **"Class II" (LS/HP) drug**
  - **pH- sensitive excipients**
  - **complex formulation (ER)**
  - **overlapping CYP 3A4/PGP substrate**
  - **significant, saturable first pass effect**
  - **F < 50%**
  - **female and male subjects**

Drug Solubility



Formulation Dissolution



Role of Excipients

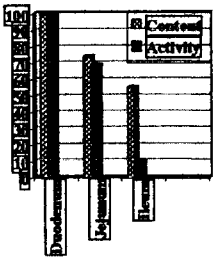
- **Rate-limiting step in absorption is *in vivo* dissolution**
- **Control release rate**
- **Different mechanisms for each Product**
- **Excipient effects in Product A pH-sensitive**

Contributions of Subjects

- **Gender differences between males and females?**
  - **focus on physiological variables**
    - **under genetic and/or environmental control**
    - **subpopulation differences in distribution**
    - **gastric/intestinal transit times, membrane permeability, luminal pH, mucosal blood flow**
    - **<u>intestinal metabolism by CYP 3A4</u>**
    - **<u>enterocyte PGP transport</u>**

Intestinal CYP 3A4

- **Large intersubject variability in substrate clearances**
- **Intrasubject < intersubject (30X) variability**
  - **influence of genetic factors > environmental factors**
- **Content and expression is site-dependent, saturable**



- **Gender differences**
  - **oral clearance < F**
  - **FPE < F**
  - **BA > F**
  - **less CYP 3A4 or homeostatic mechanism?**

Intestinal PGP

- **More limited data, particularly, gender differences**
  - increasing gradient in content/activity from proximal segment to distal segment of gut
  - saturable
  - dose-dependent effective permeability
  - activity in M > F

Mechanistic Hypothesis

- **SxF with Product B**
  - slower dissolution at pH 4.5
  - faster & more complete dissolution at pH 6.8
  - larger fraction of dose released in ileum
    - lower CYP 3A4 content & activity
      - readily saturable
    - gender differences in PGP efflux (F < M)
  - greater absorption, higher Cmax & AUC
    - [concentration x residence time]

Supportive Evidence

- **[M/P] AUC ratio for Product B**
  - **10/13 F had lower ratio**
  - **2/12 M had lower ratio**
- **Similar SxF observed in multiple dose BE study**
  - higher AUC & Cmax for Product B in F
- **Literature**
  - lower oral clearance of CYP 3A4 substrates in F

Conclusions

- **Need to collect more data to understand the mechanistic basis of SxF**
- **Additional experience with replicate BE study designs in subject subgroups will provide data sets relevant to SxF**
- **Stepwise analysis of drug, excipient, formulation and subject factors will lead to better understanding of SxF**

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