

# **Subject-by-Formulation Interaction**

## **Examples**

## Subject-by-Formulation Interaction

### *Example 1\**

- ◆ Calcium Ion Influx Inhibitor
- ◆ Immediate-release tablets (80 mg)
- ◆ Two generics and a brand name product
- ◆ Multiple-dose, 80 mg twice-a-day
- ◆ Healthy, young volunteers (18-45 years, n = 8), and hypertensive, elderly volunteers (> 65 years, n = 8)
- ◆ Presence of an age-based S x F interaction for Generic 1.

\*Reference: Carter BL et al., Pharmacotherapy, 13, 1993

## Calcium Ion Influx Inhibitor

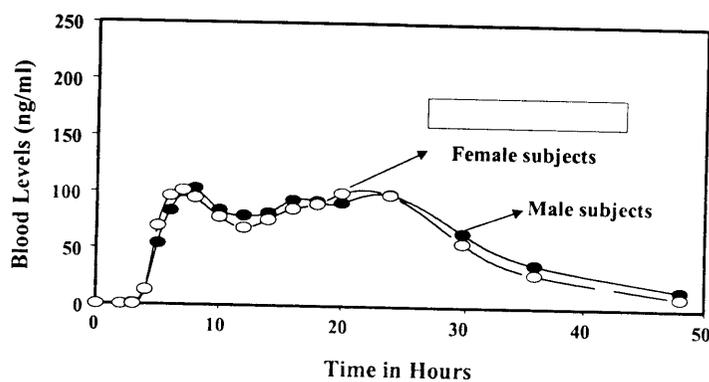
### *Age-based SxF Interaction*

<u>MEASURE</u>	<u>Subject</u>	<u>Test/Reference Ratio</u>	
		<u>Generic 1/Reference</u>	<u>Generic 2/Reference</u>
AUC <sub>0-12</sub>	Elderly	1.43	1.04
AUC <sub>0-12</sub>	Young	0.998	0.995
AUC <sub>0-24</sub>	Elderly	1.46	1.06
AUC <sub>0-24</sub>	Young	1.00	0.97
C <sub>max</sub>	Elderly	1.77	1.04
C <sub>max</sub>	Young	0.93	1.05

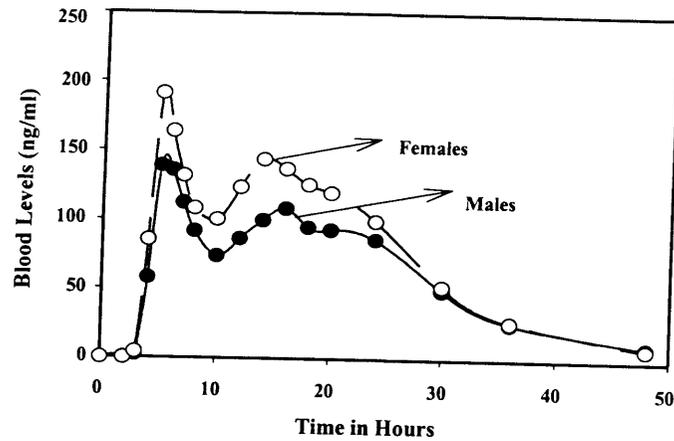
## Subject-by-Formulation Interaction *Example 2*

- ◆ Calcium channel blocking agent
- ◆ Extended-release capsules (300 mg)
- ◆ Two-way crossover, single dose, fasting BE study
- ◆ Healthy, young males (n = 12) and females (n = 13)
- ◆ Presence of a gender-based subject-by-formulation interaction

## Mean PK Profiles for Test Product



## Mean PK Profiles for Reference Product



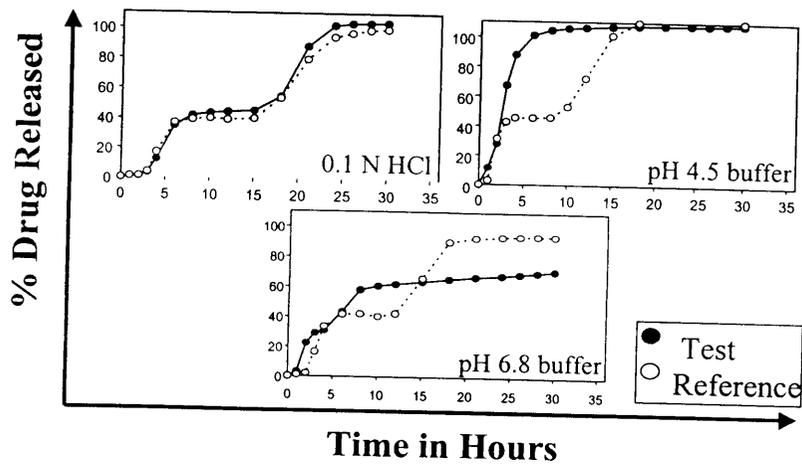
## Gender-based SxF Interaction *Single Dose*

	Mean Cmax (%CV)	Mean AUC (%CV)
<b>Males</b>		
Product T	129 ng/ml	3102 ngxhr/ml
Product R	147	2953
Overall % CV	32.1	34.5
→ T/R Ratio	0.92	1.11
<b>Females</b>		
Product T	129 ng/ml	2785 ngxhr/ml
Product R	201	3549
Overall % CV	19.8	14.4
→ T/R Ratio	0.62	0.77

## Gender-based SxF Interaction *Multiple-Dose*

	Mean Cmax	Mean AUC
<b>Males</b>		
Product T	193 ng/ml	2973 ngxhr/ml
Product R	218	2953
→ T/R Ratio	0.89	1.01
<b>Females</b>		
Product T	197 ng/ml	2915 ngxhr/ml
Product R	340	4014
→ T/R Ratio	0.58	0.73

## Calcium Channel Blocker *In Vitro Dissolution*



## **Calcium Channel Blocker**

### ***Mechanistic Basis of SxF Interaction***

---

- ◆ **Metabolism and transport**
  - Intestinal cytochrome P450 3A4 metabolism
  - P-glycoprotein transport
- ◆ **T releases more drug in proximal gut**
  - Similar enzyme binding ( $K_m$ ), capacity ( $V_m$ ) and residence time between genders
  - Similar T/R ratio for AUC and  $C_{max}$  in M and F
- ◆ **R releases more drug in distal gut**
  - Gender-related differences in intestinal metabolism and/or p-glycoprotein efflux
  - Lower T/R ratio for AUC and  $C_{max}$  in F

## **Subject-by-Formulation Interaction**

### ***Example 3***

---

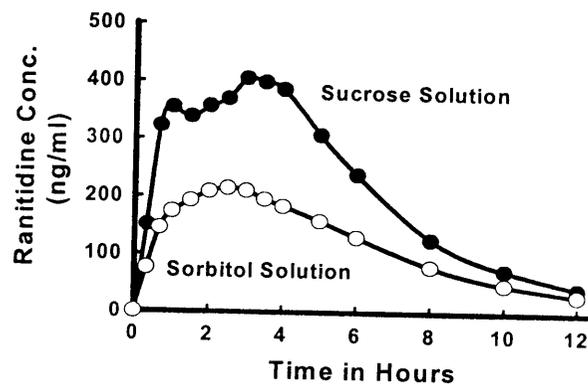
#### Excipient Effect

- ◆ Excipients with low permeability such as sorbitol or mannitol in amounts used in typical syrup formulations can significantly reduce the bioavailability of a drug that also exhibits low intestinal permeability (e.g., ranitidine).
- ◆ Subject-by-formulation interactions can occur when two syrup formulations contain different sweetening agents, e.g., sorbitol versus sucrose.

## Ranitidine Study

- ◆ Single-dose, four-way, replicate design, crossover with one week washout period
- ◆ 20 healthy volunteers (17 males, 3 females)
- ◆ 150 mg ranitidine in 15 ml sorbitol or sucrose solution administered followed by 120 ml water
- ◆ Serial blood samples collected and serum ranitidine levels determined using a validated HPLC method

## Ranitidine Levels



# Ranitidine in Sucrose vs. Sorbitol Solution

## *Subject-by-Formulation Interaction*

