Biopharmaceutics Classification System (BCS): A Regulatory Risk Management Tool

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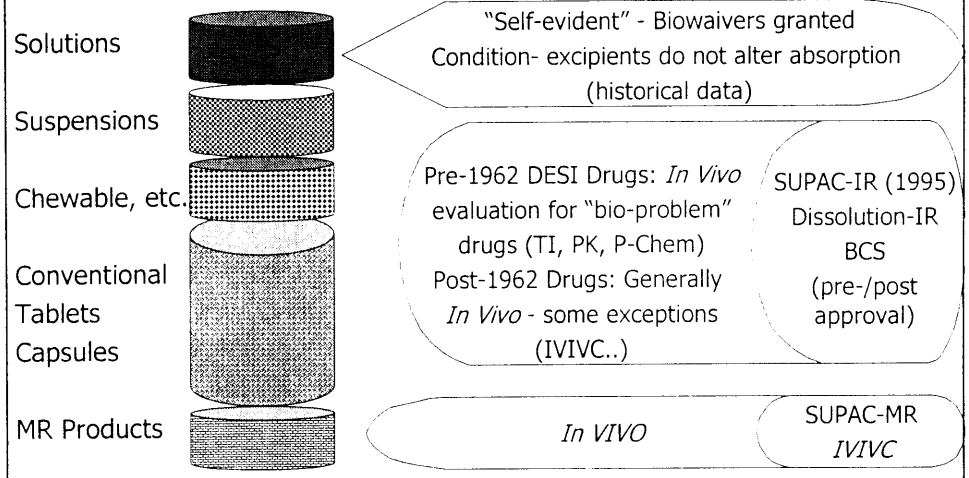
Regulatory Bioequivalence: An Overview



Bioequivalence Hearing of 1986

- "..seems sensible to think that swallowing something that turns into a solution rapidly would be difficult to lead to differences from one product to the next....."
  - Bob Temple in response to Arnold Becketts presentation
- "....I've learned that there is no support here for attempting to provide such assurance solely with *in vitro* data."
  - Milo Gibaldi

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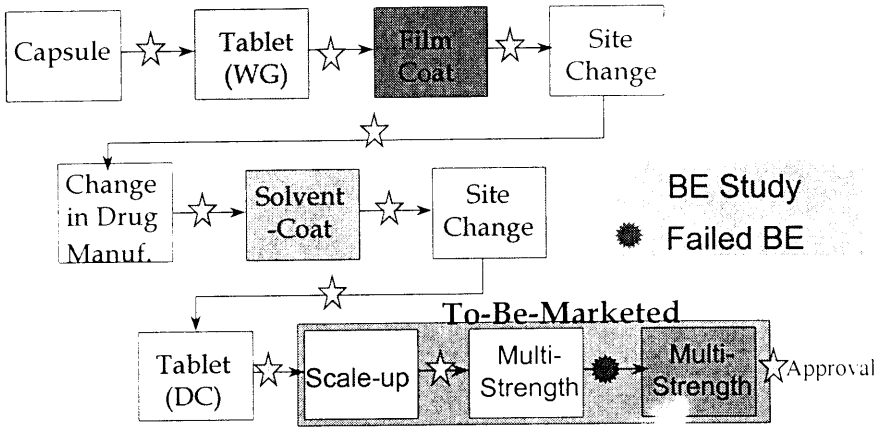
In Vivo BE* for Justifying Changes During Development



*Generally 3-6 clinical bioequivalence tests are conducted in a NDA

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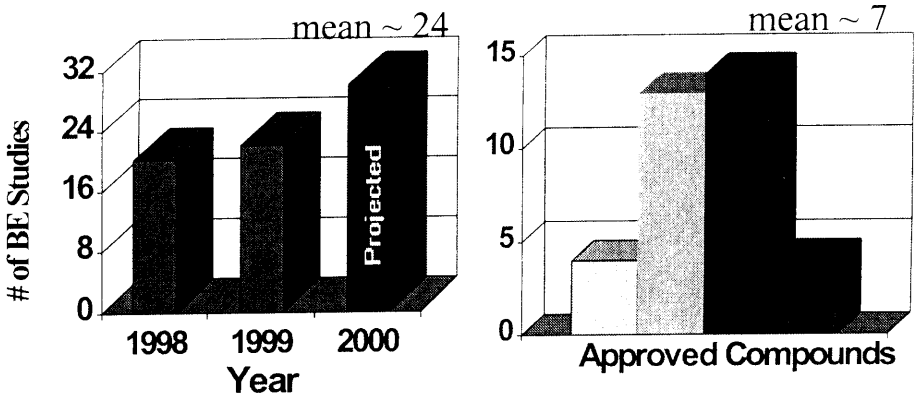
Average # of BE Studies: At a Major Pharmaceutical Company



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Need to Reduce Our Reliance on *In Vivo* BE Studies: Why?

- Ethical reasons
  - 21 CFR 320.25(a) "... no unnecessary human research should be done."
  - Science continues to provide new methods to identify and eliminate unnecessary *in vivo* BE studies
- Focus on prevention - "building quality into products" - "right first time"
- Time and cost of drug development and review

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Prior to SUPAC-IR/BCS

- *in vivo* bioequivalence (BE) assessments to justify (a majority of) manufacturing changes
- preferred use of "prior approval supplement" process to implement changes

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BCS: Regulatory History

1990	Research (FDA, MPA,Univ. Michigan, Uppsala, and Maryland)
11/1995	Application in SUPAC-IR Guidance
4/1996	BCS Working Group formed to develop a guidance
8/1996	ACPS Discussion
4/1997	AAPS/CRS/FDA Workshop
6/1997	EUFEPS 4th Int. Conference on Drug Absorption
10/1997	"Expert Panel" Meeting
12/1997	ACPS Discussion
8/1998	AAPS Workshop on Permeability Methods
10/1998	ACPS Discussion
2/1999	Draft Guidance Published
6/2000	Internal Training
8/2000	Final Guidance Published
9/2000	External Training
	Next Steps

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Next Steps

- New BCS Technical Committee
  - Chair: Lawrence Yu
  - Address implementation questions
  - Database and prospective research for extensions (links to PQRI and FIP)
    - Class III and Class II drugs
- Further research (FDA)
  - Extension of BCS based biowaivers
    - Waiver of "fed" bioequivalence studies
- Continuation of educational initiatives
  - practitioners and public
- International harmonization

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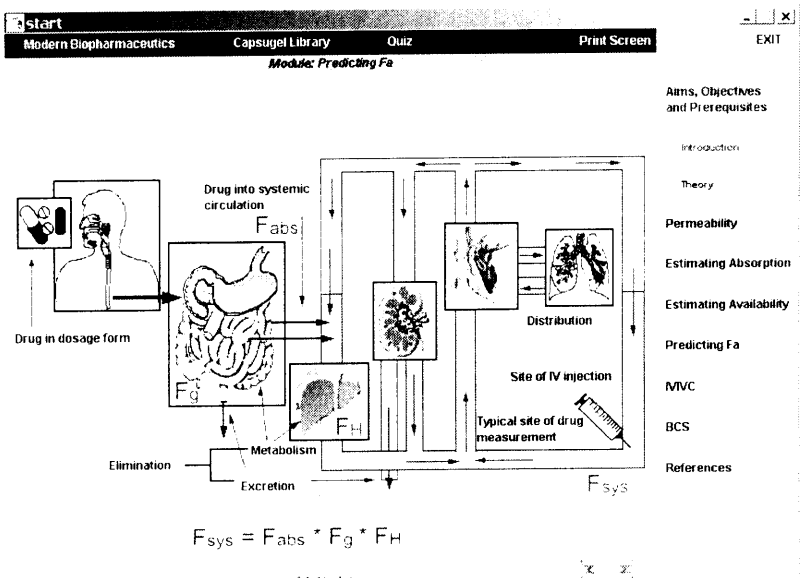
Systemic vs. Gut View



Professor Gordon Amidon, University of Michigan

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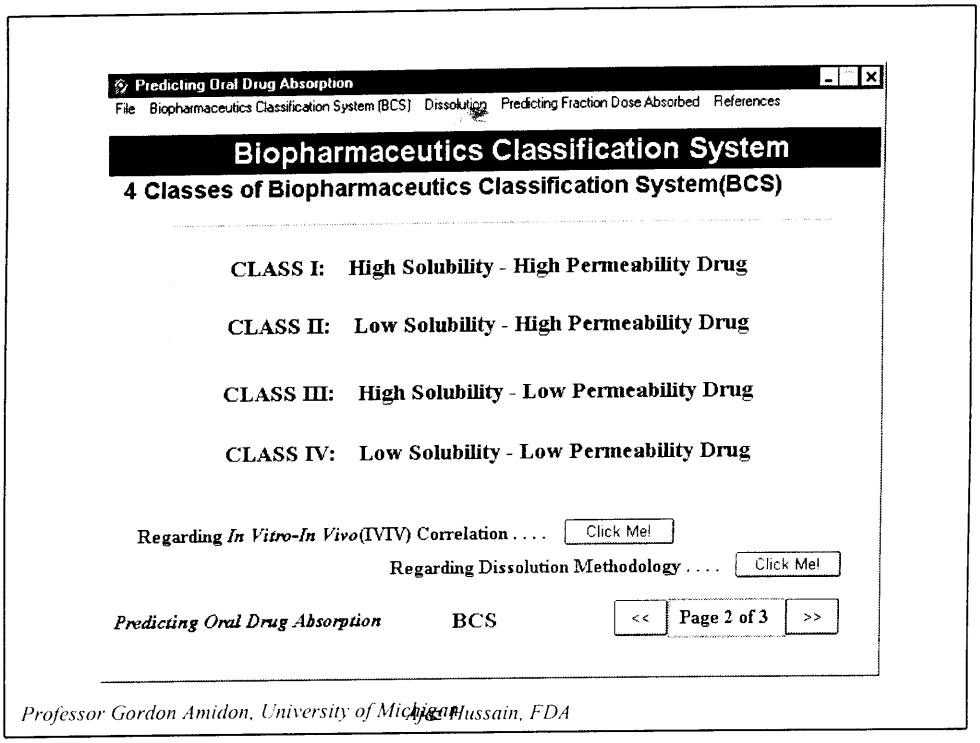

SUPAC-IR/BCS: For some 'Level 2' Changes

	HS/HP	*LS/HP*	*HS/LP*	*LS/LP*
Critical Process	Gastric Emptying	Dissolution	Permeability	D/P
IVIVC	Not likely	Likely	Not likely	(?)
Method	0.1 N HCl	pH 1 - 7.4	App/Comp	In Vivo BE
Acceptance Criteria	Single point 85% in 15 min	Multiple profiles (f2 > or = 50)	Single profile (f2 > or = 50)	AUC & Cmax 90% CI 80-125%

Note: NTI drugs excluded for some Level 2 Changes

Waiver of *in vivo* BE studies based on BCS (8/30/2000)

- Recommended for a solid oral Test product that exhibit ***rapid*** (85% in 30 min) and ***similar*** *in vitro* dissolution under specified conditions to an approved Reference product when the following conditions are satisfied:
  - Products are ***pharmaceutical equivalent***
  - Drug substance is ***highly soluble*** and ***highly permeable*** and is not considered have a ***narrow therapeutic range***
  - Excipients used are not likely to effect drug absorption

BCS: Class Membership

- High Solubility
  - the highest dose strength is soluble in ≤250 mL aqueous buffers over pH range of at 37°C.
- High Permeability
  - extent of absorption in humans is determined to be ≥ 90%
- Rapid Dissolution
  - ≥ 85% dissolves within 30 minutes in 0.1 HCl (or SGF), pH 4.5, and pH 6.8 buffers (or SIF) using Apparatus I at 100 rpm or Apparatus II at 50 rpm.

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Risk of Bio-in-equivalence

- Risk factors
  - Manufacturing changes pre/post approval
    - minor - moderate - major changes
  - Poor process capability
    - high between and within batch variability
  - Reliance on *in vitro* dissolution tests
    - single point specification - sampling - predictability
  - Other factors
    - deficiencies in BE study design - Type II error

Bioequivalence - one of the critical links between quality and S&E

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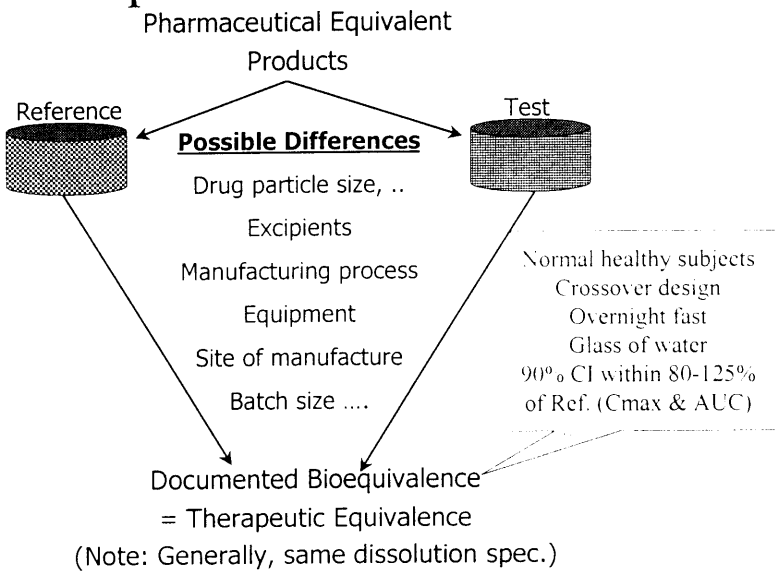
Bioequivalence: IR Products



BCS a tool for risk management

- Assessment of risk
  - What is the risk of bio-in-equivalence between two pharmaceutical equivalent products when *in vitro* dissolution test comparisons are used for regulatory decisions?
    - Likelihood of occurrence and the severity of the consequences?
- Regulatory Decision
  - whether or not the risks are such that the project can be persued with or without additional arrangements to mitigate the risk
- Acceptability of the Decision
  - is the decision acceptable to society?

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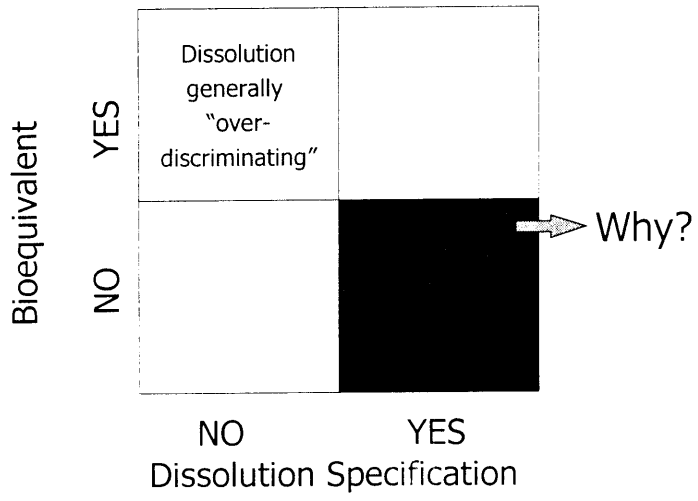
Dissolution Test & Bioequivalence: Risk Assessment



Minimizing Risk of Bio-in-equivalence

- Does *in vitro* dissolution process emulates *in vivo* dissolution process?
  - Dosage form disintegration, dissolution and stability
    - Gastrointestinal fluid volume, composition, and hydrodynamic conditions
    - Residence time (undissolved and dissolved drug) in stomach and small intestine
- Impact of excipients differences on GI physiology - drug bioavailability?

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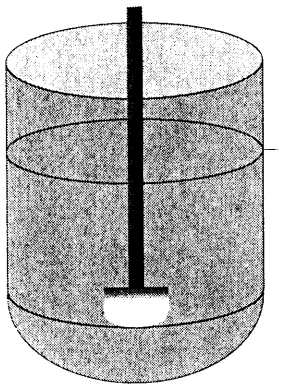
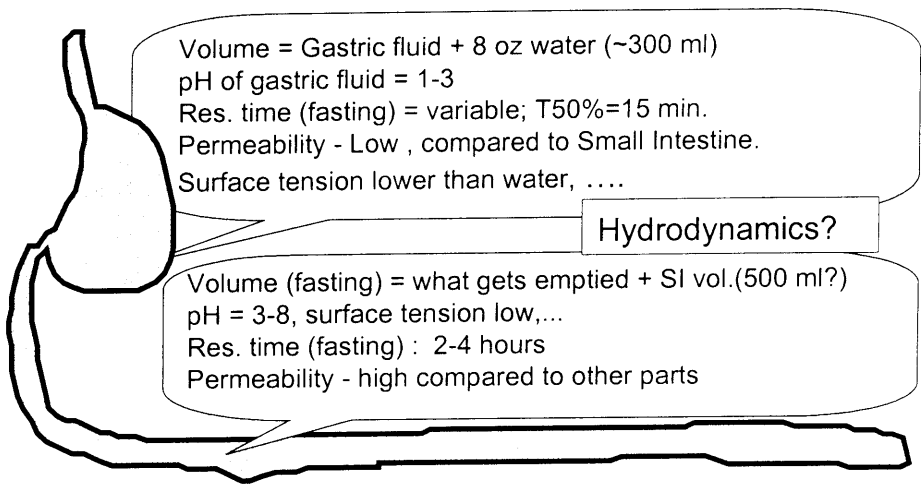
Dissolution Test Methods



> 900 ml, 37°C
> Water, 0.1 N HCl, pH 6.8 buffer, or...
> 50 rpm (paddle), 100 rpm (basket),...
> Vessel geometry
> Location of dosage unit

Typical Physiologic Parameters:
Single Dose Fasting BE Study



Dissolution tests: Debates

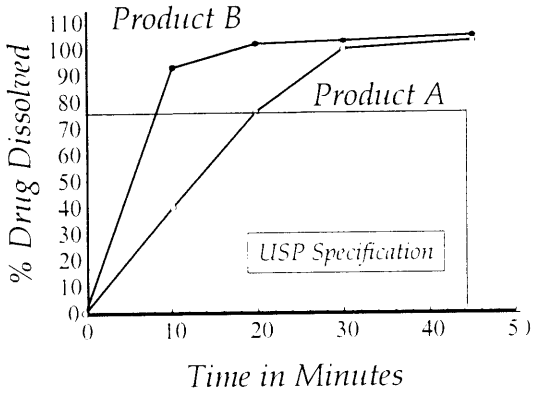
- Dissolution tests are "over discriminating"
- Products that dissolve about 70% in 45 minutes have no medically relevant bioequivalence problems
- Dissolution tests are not sufficient to assure bioequivalence
- Demonstration of IVIVC is necessary
- IVIVC's are "Product Specific"

Dissolution Test Problems: False +ives and -ives

	Test/Ref. Mean				
	15 min	*30 min*	*45 min*	*AUC*	*Cmax*
Ref	95	96	98	100	100
B	96	97	97	104	95
C	62	84	92	84	55
D	82	94	95	88	87
E	103	103	103	112	120
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

I. J. MacGilvery. Bioequivalence: A Canadian Regulatory Perspective. In. Pharmaceutical Bioequivalence . Eds. Welling, Tse, and Dighe. Marcel Dekker, Inc., New York. (1992)).

Failure to Discriminate Between Bio-in-equivalent Products: Inappropriate Acceptance Criteria



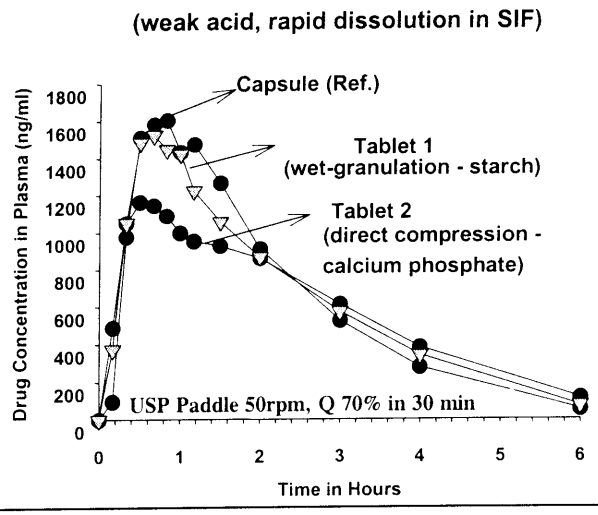
Product B was not bioequivalent to Product A

Log(AUCinf): CI 94.6 - 123.6

Log(AUC): CI 89.1 - 130.0

Cmax: CI 105.3 - 164.2

Failure to Discriminate Between Bio-in-equivalent Products: Inappropriate Test Method?



NDA #X: Bioequivalent?

- Drug X (100 mg dose, volume required to dissolve the dose at pH 8, lowest solubility, is 230 ml, extent of absorption from a solution is 95%)
- Weak base exhibits a sharp decline in solubility with increasing pH above 3
- Clinical-trial formulation: Wet granulation, drug particle size (D50%) 80 microns, lactose MCC, starch, Mg-stearte, silicon dioxide. Tablet weight 250 mg. Dissolution in 0.1 N HCl 65% in 15 min and 100 % in 20 minutes. Disintegration time 10 minutes.
- The company wants to manufacture the product using direct compression.
- To-Be-Marketed formulation: Direct compression, drug particle size (D50%) 300 microns, dicalcium phosphate, MCC, Mg-stearate, silicon dioxide. Tablet weight 500 mg. Dissolution in 0.1 N HCl - 85% in 15 min., and 95% in 20 min. Disintegration 1 min.
- Clincal product exhibits poor dissolution in pH 7.4 media (about 30% in 60 minutes). Data for T-b-M not available.

In Vitro & In Vivo Dissolution

- Dissolution methods evolved over last thirty years - reproducible test method for lot-lot quality assurance
  - Dissolution media volume and composition selected to maintain "sink" conditions
    - *In vivo* dissolution is a complex process (e.g., pH profile, bile concentration, motility patterns)
    - *In vivo* "sink" condition created due to intestinal permeability

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In Vitro - In Vivo Correlations

- When dissolution is slow (rate limiting) *IVIVC* have been demonstrated, however such a correlation may not hold when certain formulation changes are introduced
  - For ER products a change in release mechanism
  - For IR products of low solubility drugs (e.g., spirinolactone and carbamazepine)

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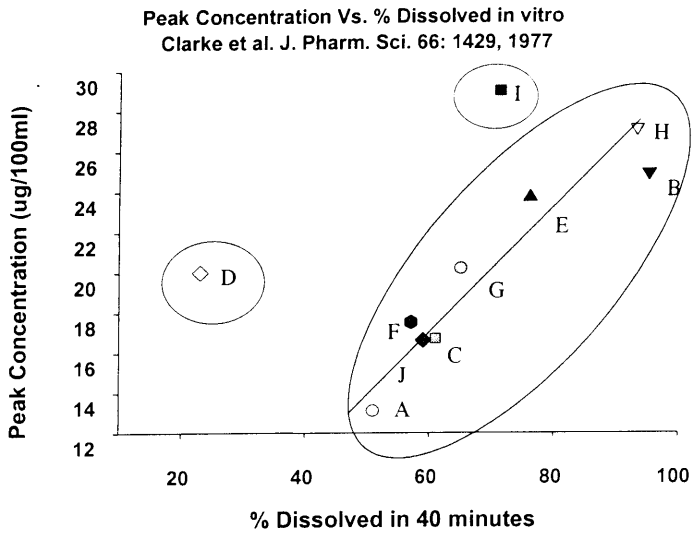
"Formulation Specific" IVIVC



Reliance on current dissolution practice can poses an unacceptable level of risk

- Compared to high solubility drugs, risk is higher for low solubility drugs
- Products with slow or extended dissolution profiles pose a higher risk (dissolution rate limiting)
  - Need for a rapid dissolution criteria
- Potential for significant differences between *in vivo* and *in vitro* "sink" conditions higher for low permeability drugs

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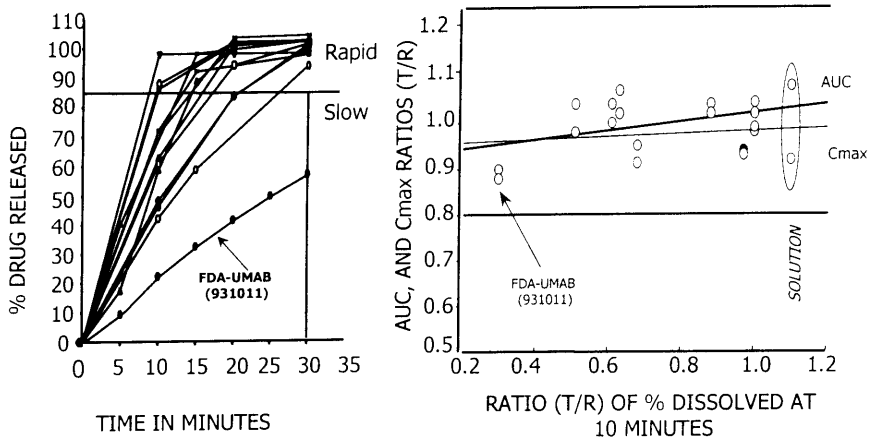
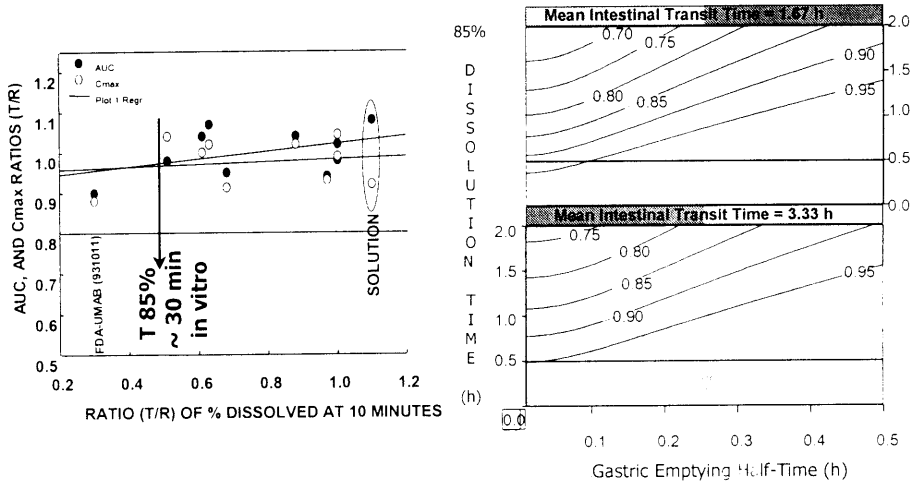
Metoprolol IR Tablets: In Vitro - In Vivo Relationship



Metoprolol IR Tablets: Experimental & Simulation Data



Risk Factor: Excipients

- Is the [current] approach of evaluating excipients for decisions related to biowaiver of oral solutions sufficient?

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Sorbitol/Mannitol: Impact on Bioavailability

- 2.3 grams of mannitol in a chewable tablet reduced bioavailability of cimetidine (a low permeability drug, per FDA's BCS Guidance) compared to a tablet containing the same amount of sucrose
  - AUC, Cmax , and Tmax ratios of the mean values were 71%, 46%, and 167%, respectively
    - Sparrow et al. J. Pharm. Sci. 84: 1405-1409. (1995)
- About 10 grams of sorbitol had no (minimal) effect on bioavailability (Cmax and AUC) of theophylline (a high permeability drug)
    - Fassihi et al. Int. J. Pharm. 72: 175-178. (1991)

Experimental Formulations

Ingredient	Test Formulation	Reference Formulation	BCS Permeability
Ranitidine or Metoprolol	0.15 g 0.1 g	0.15 g 0.1 g	Low High
Sucrose	-	5 g	High*
Sorbitol	5 g	-	Low
Water	15 ml	15 ml	High

* Rapidly metabolized at/in the intestinal wall to glucose and fructose, both exhibit complete absorption

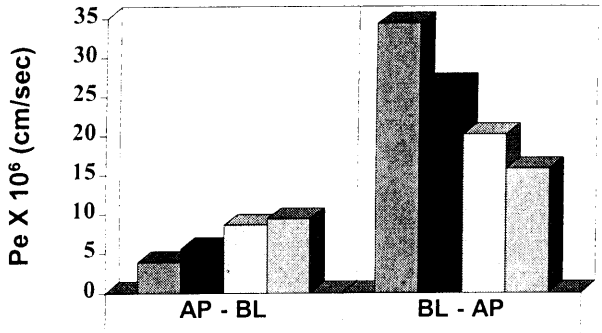
Bioequivalence Assessment

Parameter	Lower 90% CI	Upper 90%CI
Ln (Cmax)	Ran: 44% Met: 71%	Ran: 54% Met: 85%
Ln(AUCi)	Ran: 52% Met: 86%	Ran: 62% Met: 100%

Note: Solution containing sucrose was used as the reference

Polysorbate 80: $AcPhe(N\text{-}MePhe)_2NH_2$ Permeability (CACO-2)

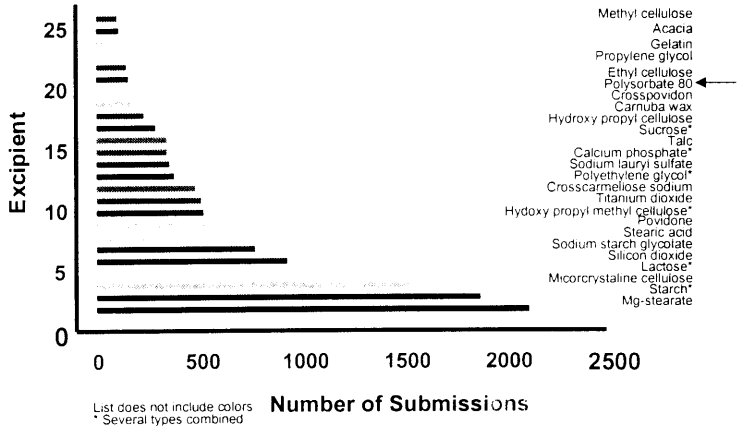
Nerurkar, Burton and Borchardt. Pharm. Res. 13: 528-534 (1996)



	AP - BL	BL - AP
None	3.85	34.31
5X10(-4) % W/V	5.62	26.52
5X10(-3) % W/V	8.58	20.11
5X10(-2) % W/V	9.44	15.82

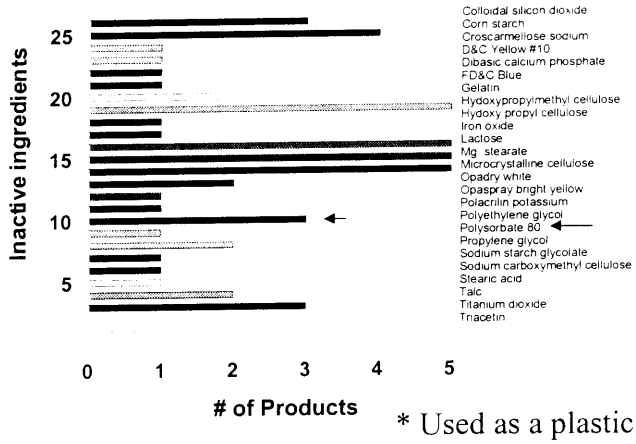
Common Excipients in IR Tablets

COMMON EXCIPIENTS IN TABLETS
(The Inactive Ingredient Guide: More than 100 submissions)



List does not include colors
* Several types combined

Impact of Polysorbate 80* on BE



* Used as a plasticizer

Risk Factor: Excipients

- Is the [current] approach of evaluating excipients for decisions related to biowaiver of oral solutions sufficient?
  - For BCS based biowaivers a higher standard was adopted (by limiting biowaivers to *highly permeable* drugs)
    - excipients used in solid oral products less likely to impact drug absorption compared to liquid oral product
  - *High permeability* attribute reduces the risk of bio-in-equivalence
    - decreased small intestinal residence time by osmotic ingredients
    - enhanced intestinal permeability (potentially by surfactants)

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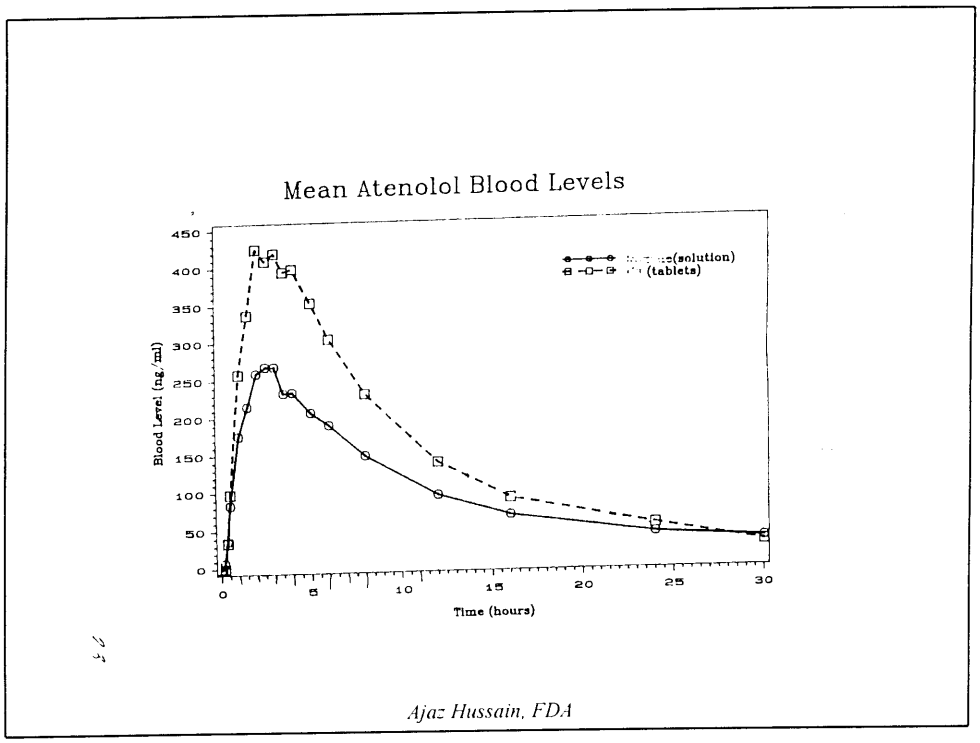
Mean Atenolol Blood Levels
(solution)
(tablets)
Blood Level (ng/ml)
Time (hours)
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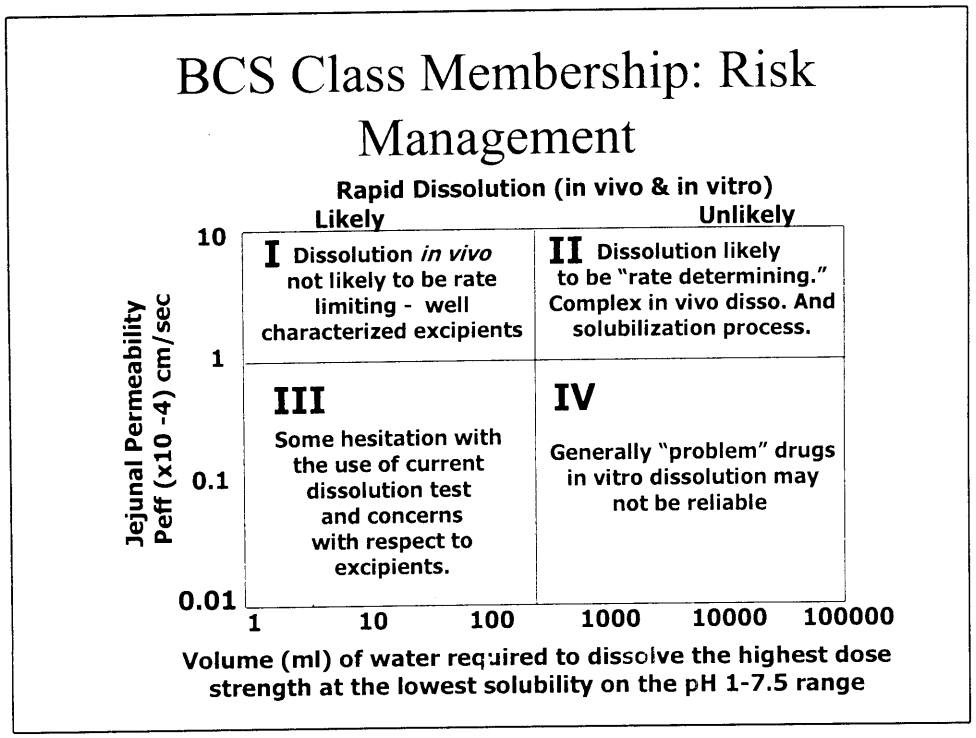
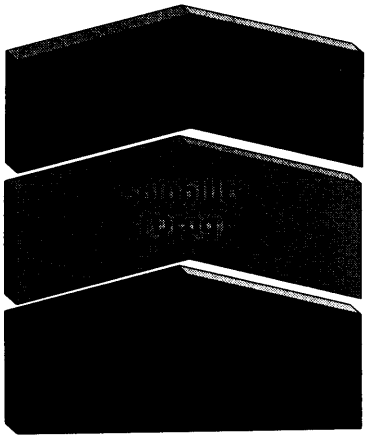

BCS Class Membership: Risk Management
Rapid Dissolution (in vivo & in vitro)
Likely
Unlikely
I Dissolution in vivo not likely to be rate limiting - well characterized excipients
II Dissolution likely to be "rate determining." Complex in vivo disso. And solubilization process.
III
Some hesitation with the use of current dissolution test and concerns with respect to excipients.
IV
Generally "problem" drugs in vitro dissolution may not be reliable
Jejunal Permeability Peff (x10 -4) cm/sec
10
1
0.1
0.01
1
10
100
1000
10000
100000
Volume (ml) of water required to dissolve the highest dose strength at the lowest solubility on the pH 1-7.5 range

BCS Class Boundaries: Objectives



Rapid dissolution - ensure that in vivo dissolution is not likely to be the "rate determining" step

High solubility - ensure that solubility is not likely to limit dissolution and, therefore, absorption

High permeability - ensure that drug is completely absorbed during the limited transit time through the small intestine

Experience with BCS based biowaivers

- Strong support from scientific community
  - ACPS, Experts, FDA staff, Public workshops
- Some concerns expressed at public workshops and comments on draft guidance
  - "overly conservative" - should also apply to Class III and some class II drugs
  - application for Generics
  - impact of excipients
- Submission activity low, higher for NDA's

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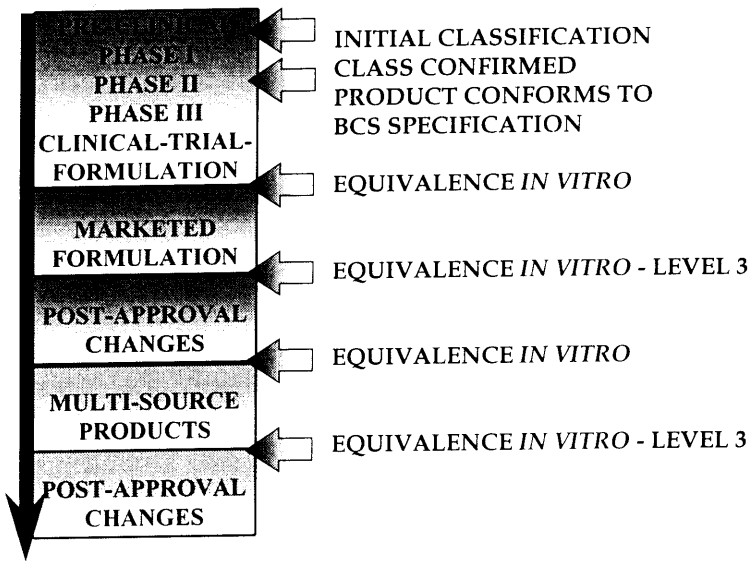
BCS Applications



Connecting-the-Dots: Discovery-Development - Review