The BCS and Biowaivers

An overview

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Outline

- **Introduction**
  - Fundamentals of the BCS
  - BCS additions and improvements
- **Biowaivers**
  - Example of a weak base
  - Snap shot in the Americas
    - Zidovudine
    - Amoxicillin
    - Metronidazole
- **Conclusions**

Formulation and PK

- **Biopharmaceutics** has been defined as the study of the influence of **formulation factors** on the **therapeutic activity** of a drug product.
- Pharmacokinetics is the study of those rate processes involved in the absorption, distribution, metabolism and excretion of drugs.

Differences in Biopharmaceutics

Differences in Pharmacokinetics

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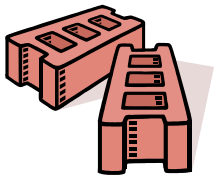
Fundamental 1

Only what is dissolved can be absorbed



Fundamental 2

Only what is absorbed can be studied in vivo

Biopharmaceutical Drug Classification System (BCS)

Class	Solubility	Permeability
I	High	High
II	Low	High
III	High	Low
IV	Low	Low

Solubility directly influences the dissolution behavior of oral dosage forms in gastrointestinal tract

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Biopharmaceutics Classification System

Dose Number

A function of solubility of drug substance

$$Do = \left(\frac{D / V_{Water}}{C_S} \right)$$

Solubility Issues

$D / V_{water} >> C_S$ ~ *High Do* $D / V_{water} << C_S$ ~ *Low Do*

BCS: which solubility is the right one?

- Solubility in water/buffers
- Solubility in gut juices
- Formulation - drug solubilization

Biopharmaceutics Classification System Dissolution number

Diffusivity $5x10^{-6}$ cm^2/s

Solubility *mg/mL*

$$Dn = \left(\frac{3D}{r^2} \right) \left(\frac{C_S}{\rho} \right) (T_{GI}) = \left(\frac{T_{GI}}{T_{DISS}} \right)$$

Particle Radius *25 mm*

Density *1.2 mg/cm³*

Residence time in GI *180 min*

Time required for complete dissolution

Biopharmaceutics Classification System Absorption number

Effective permeability

$$An = \left(\frac{P_{eff}}{R} \right) (T_{GI}) = \frac{T_{GI}}{T_{ABS}}$$

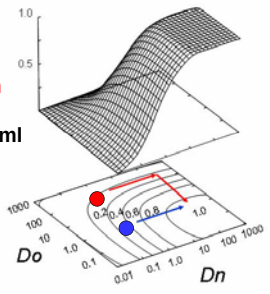
Residence time in GI

Radius of GI

Time required for complete absorption

Fraction Dose Absorbed

	Digoxin	Griseofulvin	
Dose	0.5	500	mg
C_s	0.024	0.015	mg/ml
V_{sol}	20.8	33,333	ml
Do	0.08	133	
Dn	0.52	0.32	



Three Factors of Limited Absorption

Dose Number limited ← Given / Modify

Dissolution Number limited ← Formulation

Absorption Number limited ← Given

Biopharmaceutical Risk Management Tool

Suggestions to improve the BCS

- Solubility at intestinal pH values
- BDDCS

Solubility

The "High Solubility" Definition of the Current FDA Guidance on Biopharmaceutical Classification System May Be Too Strict for Acidic Drugs" (Yazdanian et al 2004)

- Based on the current definition of solubility, 15 of the 18 acidic NSAIDs in this study will be classified as Class II compounds as the solubility criteria applies to the entire pH range of 1.2 to 7.4, although the low solubility criteria does not hold true over the entire pH range.
- Whence, of the 18 acidic drugs, 15 can be classified as Class I based on the pH 7.4 solubility alone. This finding is intriguing because these drugs exhibit Class I behavior as their absorption does not seem to be dissolution or solubility limited.

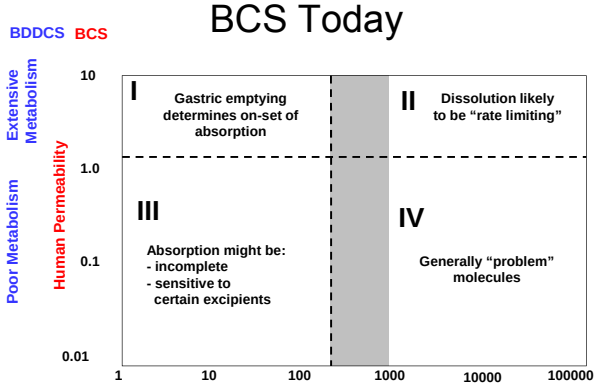
- **Recommendation: Acetic Drugs pH 5.0 – 7.4**

Biopharmaceutical Drug Disposition Classification System **BDDCS**

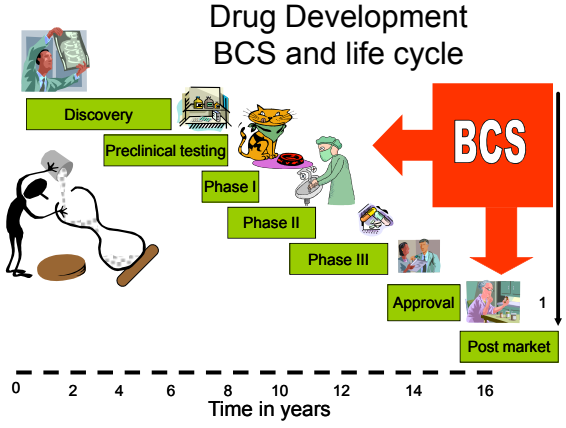
- Class 1and Class 2 compounds are eliminated primarily via metabolism
- Class 3 and Class 4 compounds are primarily eliminated unchanged into the urine and the bile
- "extensive metabolism" ≥70% metabolism of an oral dose in vivo in humans
- "poor metabolism" ≥50% of the dose be excreted unchanged.

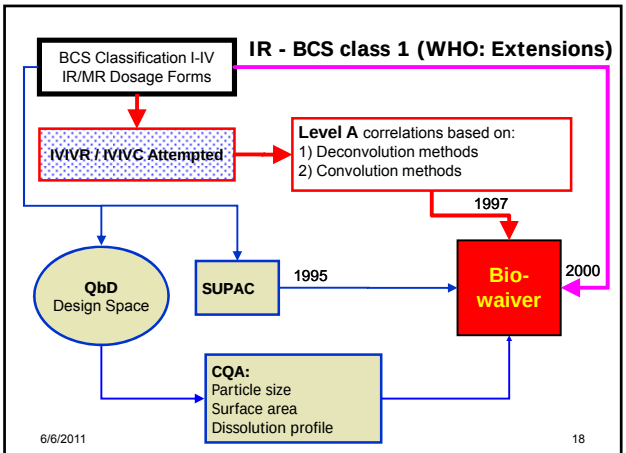
Custodio et al. 2008

BCS Today



Drug Development BCS and life cycle





basic definitions

FDA defines IVIVC as "A predictive mathematical model describing the relationship between an in vitro property of a dosage form (usually the rate and extent of drug dissolution or release) and a relevant in vivo response, e.g., plasma drug concentration or amount of drug absorbed" (FDA September 1997)

Guidance for industry, extended release oral dosage forms: development, evaluation and application of an in vitro/in vivo correlation. FDA, CDER, 1997.

Example Weak Base

- pKa = 4.6
- logP = 3.1
- Oral bioavailability is 100% (Agrawal et al, 2003)

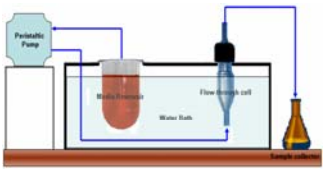
Results - Solubility & Dose/Solubility ratio

			Dose(mg)		
			60	90	120
	pH	Solubility (mg/mL)	Dose/solubility ratio (mL)		
SGF (Without enzymes)	1.2	13.21 ±1.39	4.5	6.8	9.1
Acetate Buffer	4.1	0.60 ± 0.12	100.0	150.0	200.0
Blank FeSSIF	5.0	0.22 ± 0.04	272.7	409.1	545.5
FeSSIF (with bile salts and lecithin)	5.0	0.28 ± 0.03	214.3	321.4	428.6
Blank FaSSIF	6.5	0.16 ± 0.04	375.0	562.5	750.0
FaSSIF (with bile salts and lecithin)	6.5	0.14 ± 0.03	428.6	642.9	857.1
SIF pH 6.8	6.8	0.14 ± 0.02	428.6	642.9	857.1

1. **high** solubility at low pH 1.2, **decreases** as **pH increases**
2. Solubility in biorelevant media at **pH 5.0** and **6.5** are **not significantly** different from **blank buffers**

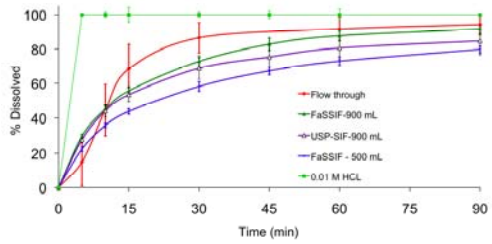
According to BCS, this drug is a poorly soluble drug

Flow-through protocol (Alberta Apparatus 4)



Designed to simulate passage of a drug through the GIT
1-SGF-SLS(0.25%) for 15 min
2-Biorelevant media pH 6.5 for 75 min
3-Biorelevant media pH 7.5 for 60 min
4-Biorelevant media, pH 5.0 for 30 min
5-Entire fluid flow per sampling interval collected
6-A sample was taken and analyzed Test time 180 min

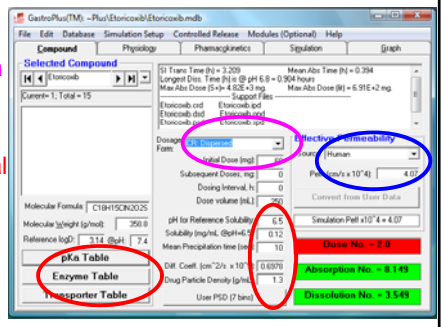
Summary: Dissolution Profiles



0.01 M HCl in the USP-2 100% in 5 min
Flow through, 94%
FaSSIF-900 mL, 91% -solubilizing effect of bile salts & lecithin
SIF 84% - poor wetting
FaSSIF-500 mL, 79% - non-sink conditions

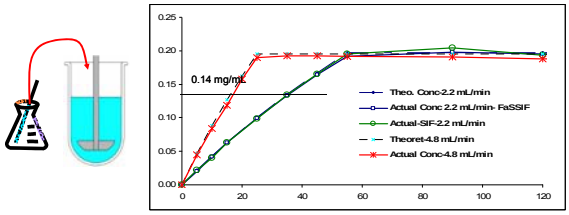
GastroPlus Software

Dissolution Data as Input
Permeability
Physicochemical Data as Input



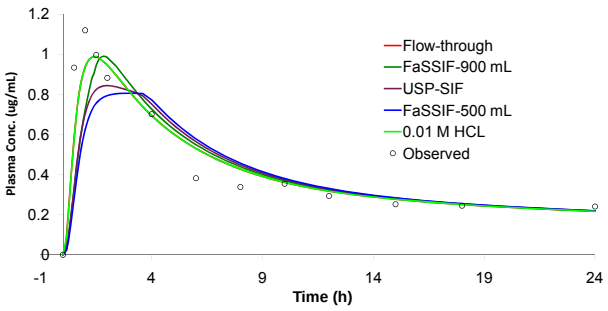
Investigating possible *in vivo* precipitation using a transfer model

1. 120 mg of Drug was dissolved in 120 mL of SGF, then pumped into 500 mL biorelevant or SIF in a dissolution vessel.
2. Possible precipitation was monitored via conc-time measurement.



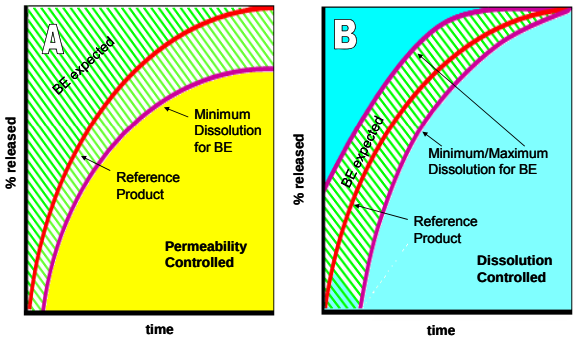
1. The drug stays solubilized when added as a solution
2. A concentration higher than predicted from equilibrium solubility is attained, without precipitation for 2 h.

Simulations results



1. All AUC are not significantly different from observed (p>0.05)
2. Cmax FaSSIF-500 mL and SIF are significantly different from observed (p<0.05

Dissolution Requirements



WHO Biowaiver

BCS Classification I-IV IR Dosage Forms

BCS class 1 Class 3 and Class 2 Weak acids

In Vitro Equivalence

Generic Drug Approval

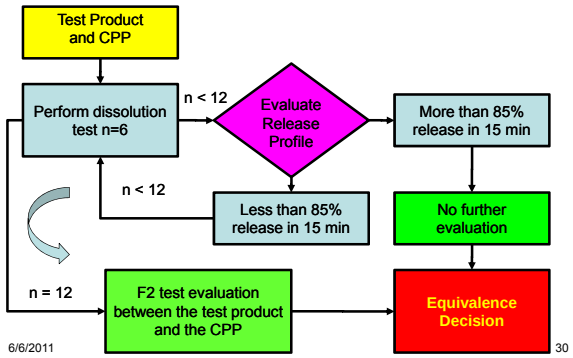
Bio-waiver

WHO EXPERT COMMITTEE ON SPECIFICATIONS FOR PHARMACEUTICAL PREPARATIONS

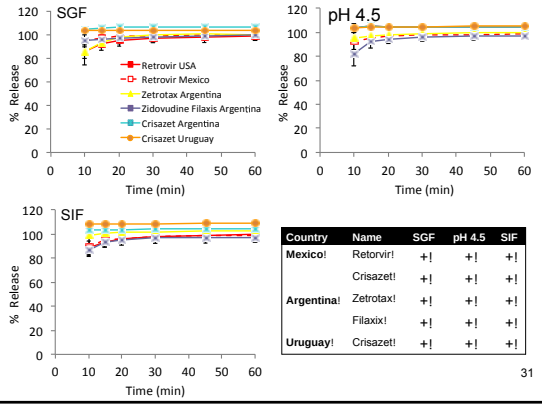
The dissolution testing is now emerging as a surrogate equivalence test for certain categories of orally administered pharmaceutical products.

For these products (typically solid oral dosage forms containing APIs with suitable properties) a comparative *in vitro* dissolution profile Similarity can be used to document equivalence of a multisource generic with a comparator product.

Study Design and Considerations



Zidovudine



Country	Name	SGF	pH 4.5	SIF
Mexico!	Retorvir!	+!	+!	+!
	Crisazet!	+!	+!	+!
Argentina!	Zetrotax!	+!	+!	+!
	Filaxix!	+!	+!	+!
Uruguay!	Crisazet!	+!	+!	+!

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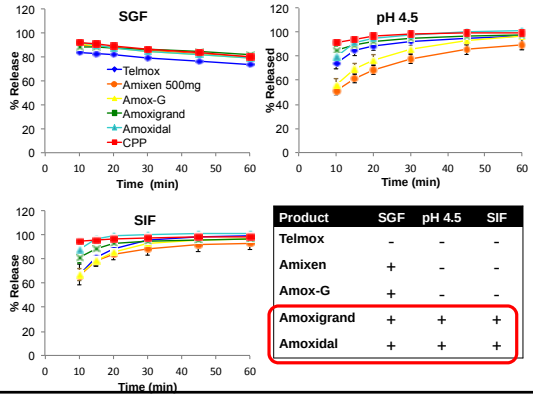
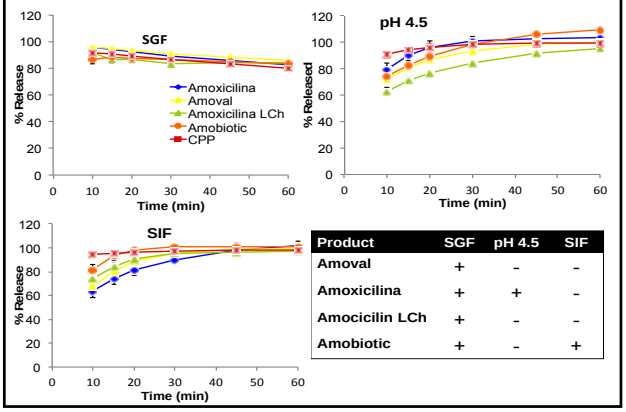
Amoxicillin Argentina



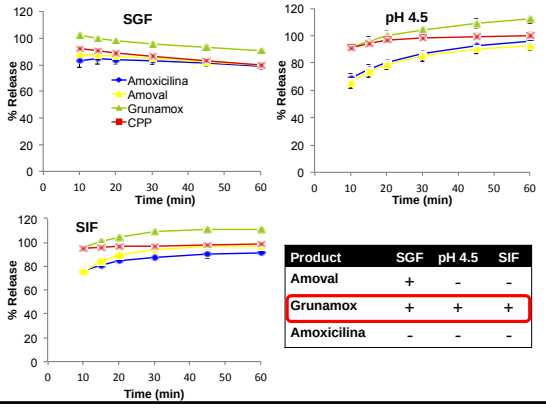
Product	SGF	pH 4.5	SIF
Telmox	-	-	-
Amixen	+	-	-
Amox-G	+	-	-
Amoxigrand	+	+	+
Amoxidal	+	+	+

Amoxicillin Chile



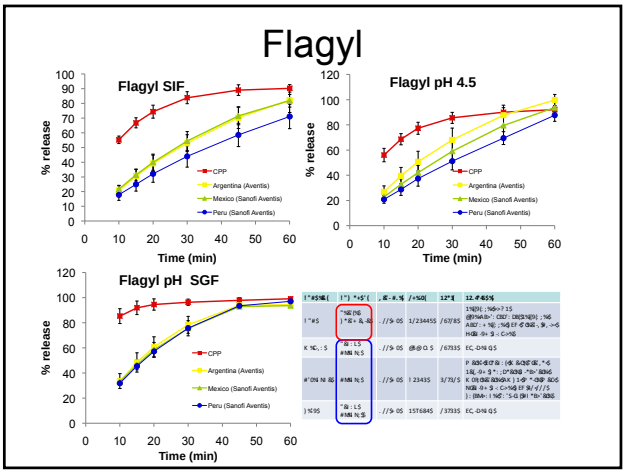
Product	SGF	pH 4.5	SIF
Amoval	+	-	-
Amoxicilina	+	+	-
Amocicilin LCh	+	-	-
Amobiotic	+	-	+

Amoxicillin Peru

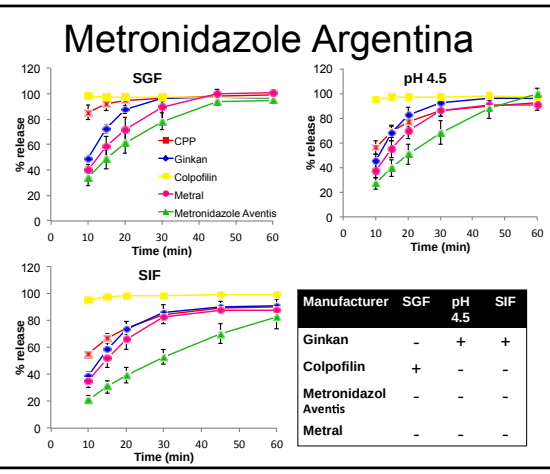


Product	SGF	pH 4.5	SIF
Amoval	+	-	-
Grunamox	+	+	+
Amoxicilina	-	-	-

Flagyl

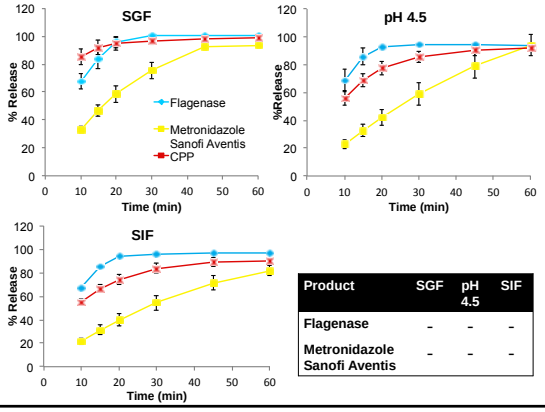


Metronidazole Argentina



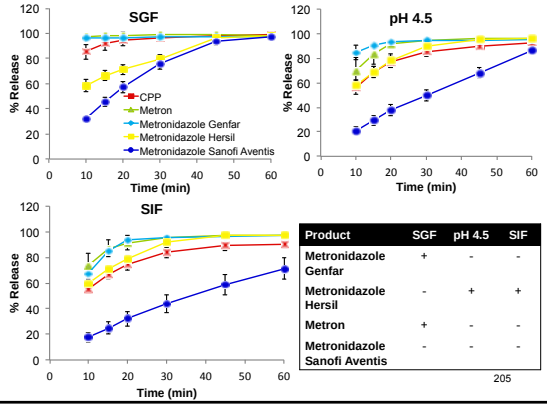
Manufacturer	SGF	pH 4.5	SIF
Ginkan	-	+	+
Colpofilin	+	-	-
Metronidazol Aventis	-	-	-
Metral	-	-	-

Mexico



Product	SGF	pH 4.5	SIF
Flagenase	-	-	-
Metronidazole Sanofi Aventis	-	-	-

Peru



Product	SGF	pH 4.5	SIF
Metronidazole Genfar	+	-	-
Metronidazole Hersil	-	+	+
Metron	+	-	-
Metronidazole Sanofi Aventis	-	-	-

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Conclusions

- The BCS changed the way we look at drugs
- Additions to the BCS have increased our understanding and the applicability of the BCS
- The BCS is the mechanistic base for modern oral drug development and can be used as
  - Riskmanagement tool in early drug development
  - Riskmanagement tool clinical development
- The BCS is the scientific foundation for Biowaivers
- Generic drugs can be approved using biowaivers

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