بسم الله الرحمن الرحيم

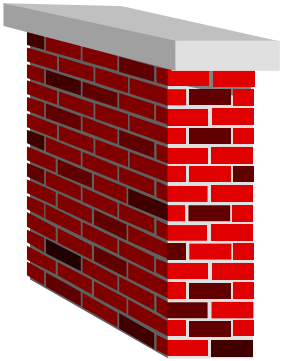
دور التصنيف الصيدلاني الحيوي في تطوير الصناعة الصيدلية

Role of Biopharmaceutical Classification System BCS in Developing Industrial Pharmacy

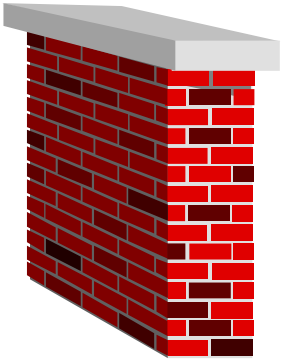
د.هند الزين
قسم الصيدلانيات

ركائز التصنيف الصيدلاني الحيوي

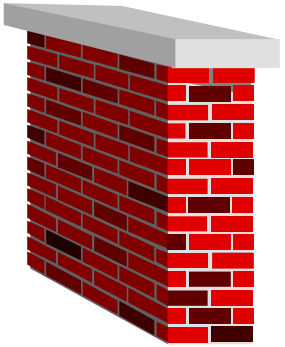
Pillars of the BCS



معدل الانحلال

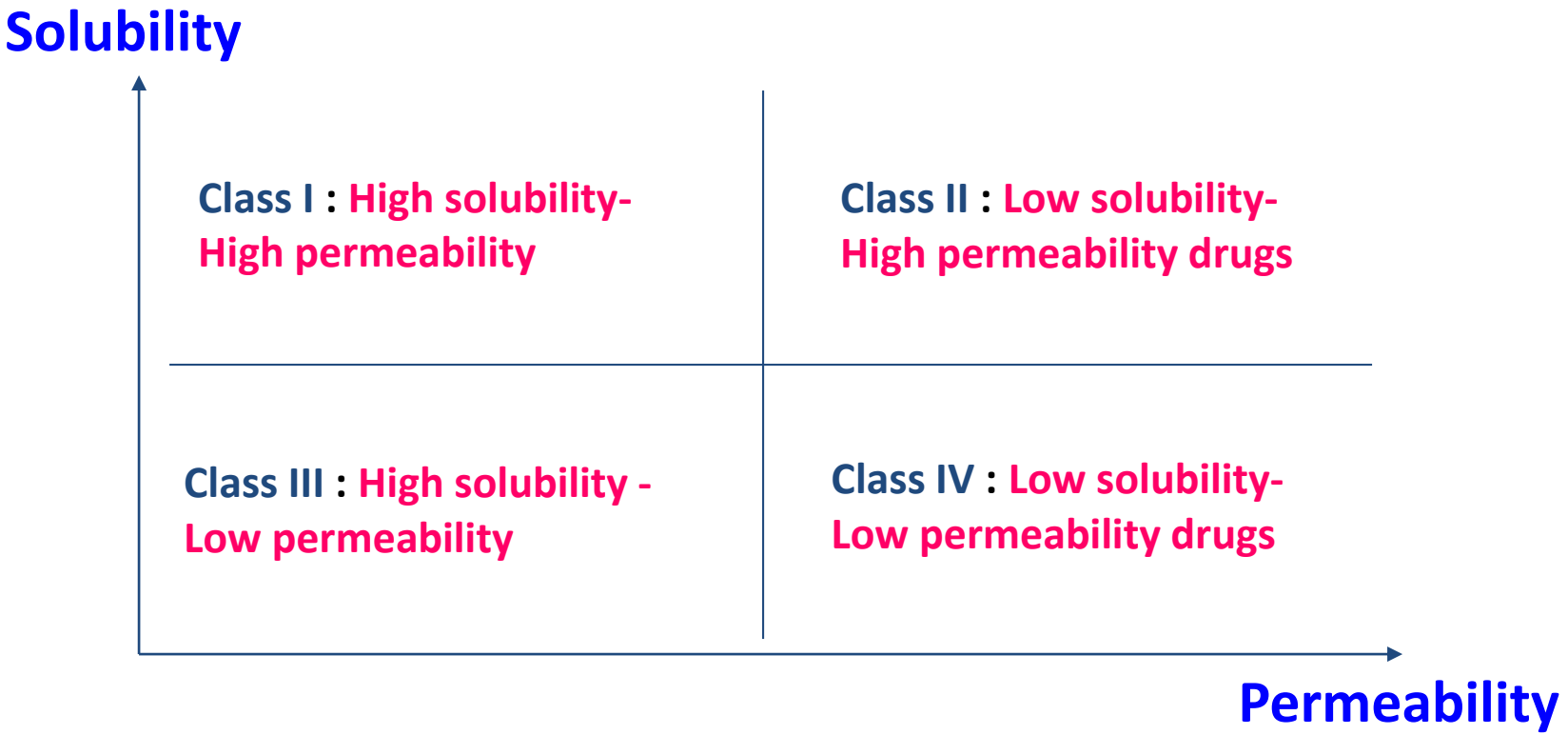


النفوذية



الذوبانية

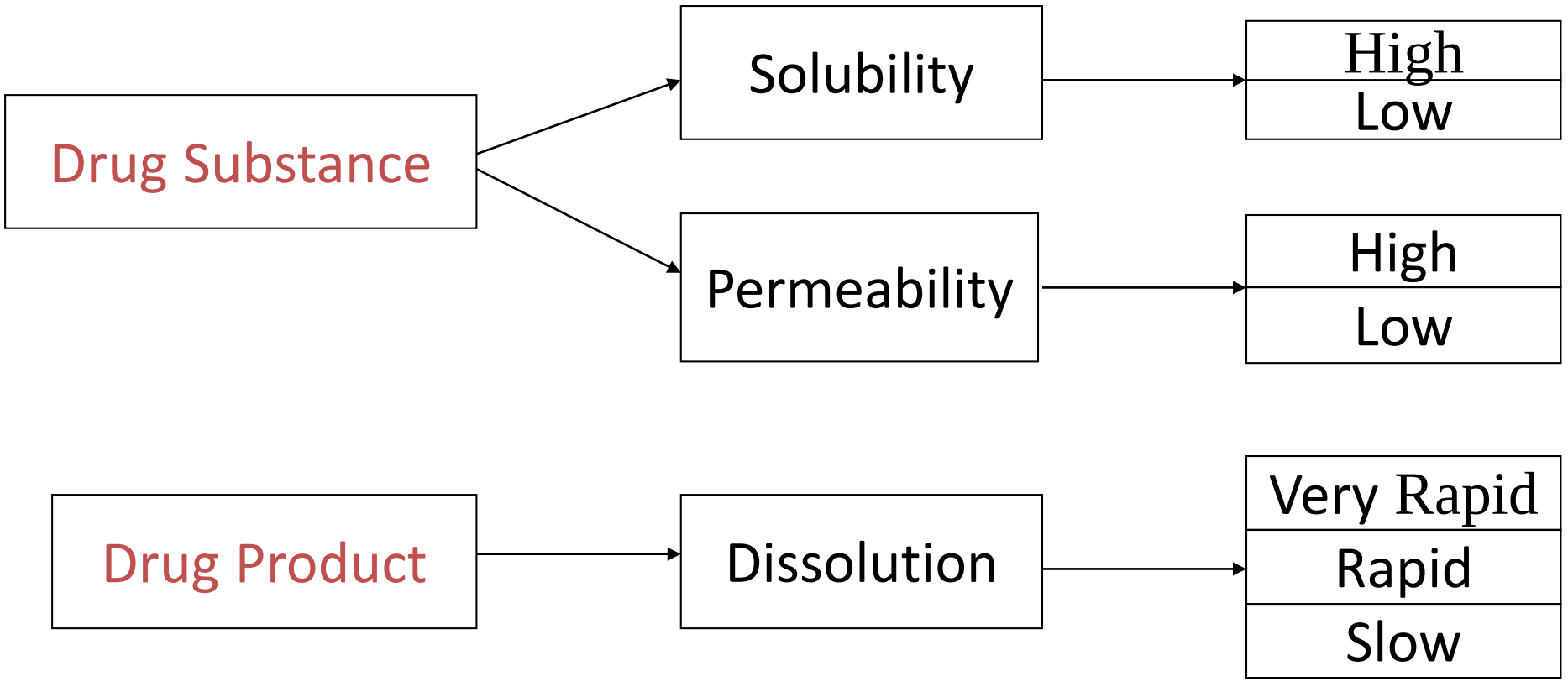
BIOPHARMACEUTICS CLASSIFICATION SYSTEM (BCS)



Biopharmaceutical Classification System

Class	solubility	permeability	comment
Class 1	High	High	Bioavailability problem is not expected for immediate release drug products
Class 2	Low	High	Bioavailability is controlled by the dosage form and rate of release of the drug substance.
Class 3	High	Low	Drug is permeability limited Bioavailability may be incomplete if the drug is not released and dissolved within absorption window.
Class 4	Low	Low	Difficulty in formulating a drug product that will deliver consistent drug bioavailability. An alternate route of administration may be needed.

BIOPHARMACEUTICS CLASSIFICATION SYSTEM (BCS)



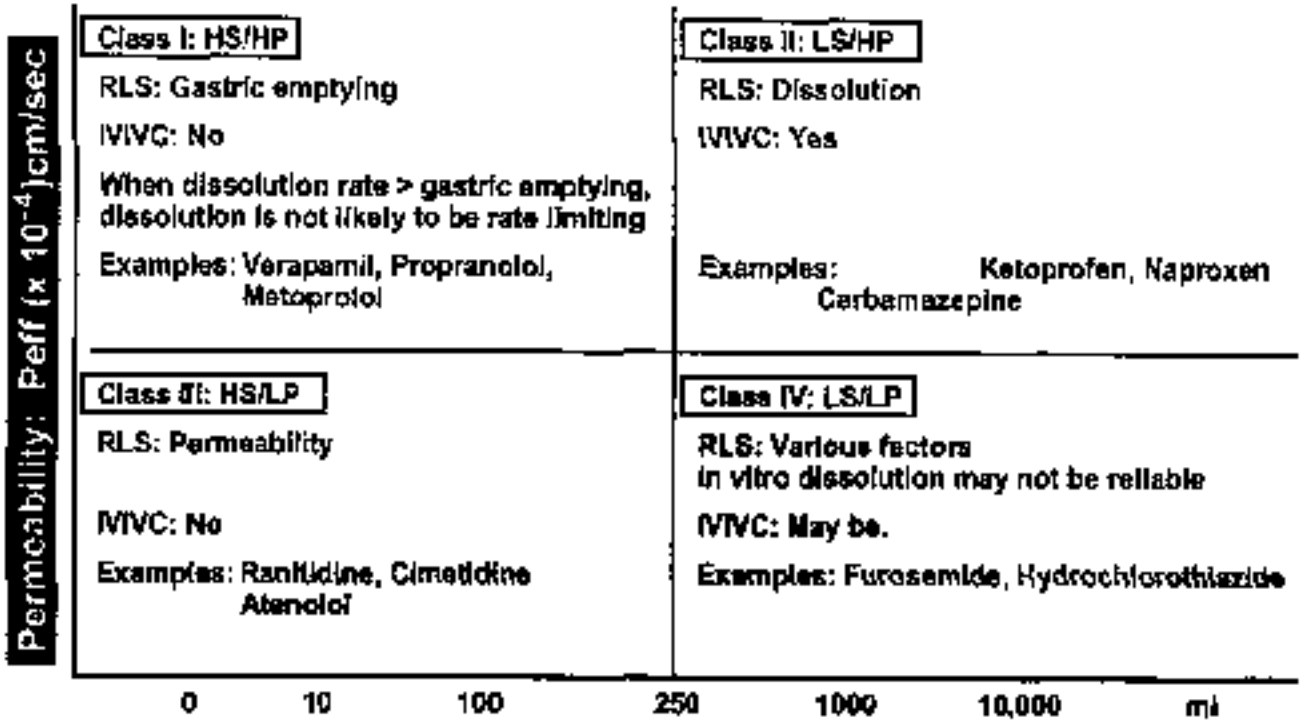
FDA BCS-BIOWAIVER GUIDANCE
Dissolution

- Very rapidly dissolving **≥ 85%** within **15 min**
- Rapidly dissolving **≥ 85%** within **30 min**
- Slowly dissolving – more than **30 min** for **85%** dissolution

BIOPHARMACEUTICS CLASSIFICATION SYSTEM (BCS)

- The successful development of medicinal products for oral use requires identification of the rate limiting step(s) of the intestinal absorption process of the active substance
- 3 major factors govern drug absorption:
  - Aqueous solubility **active substance**
  - Intestinal permeability **active substance**
  - Dissolution **oral formulation**

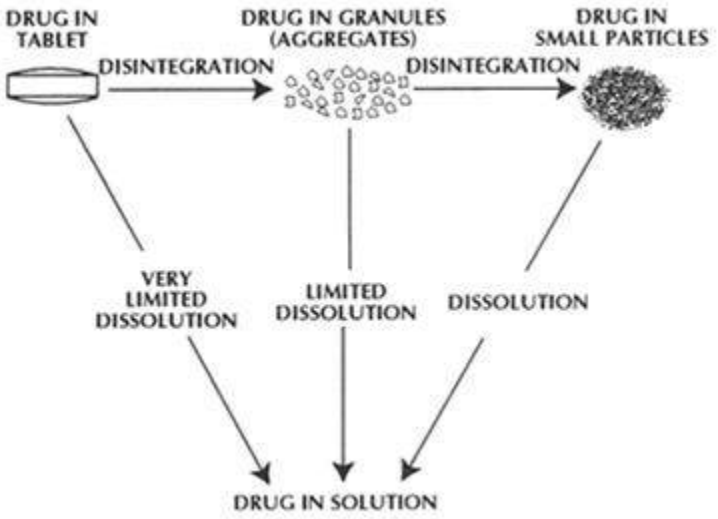
Biopharmaceutics Classification System



RLS: Rate limiting Step.

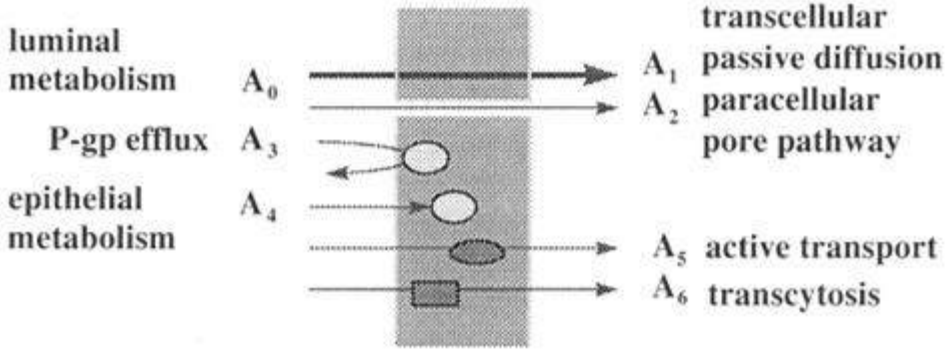
BIOPHARMACEUTICS CLASSIFICATION SYSTEM (BCS)

solubility, dissolution and permeability are the 3 major factors controlling the oral absorption of drug substances from IR oral medicinal products



Solubility

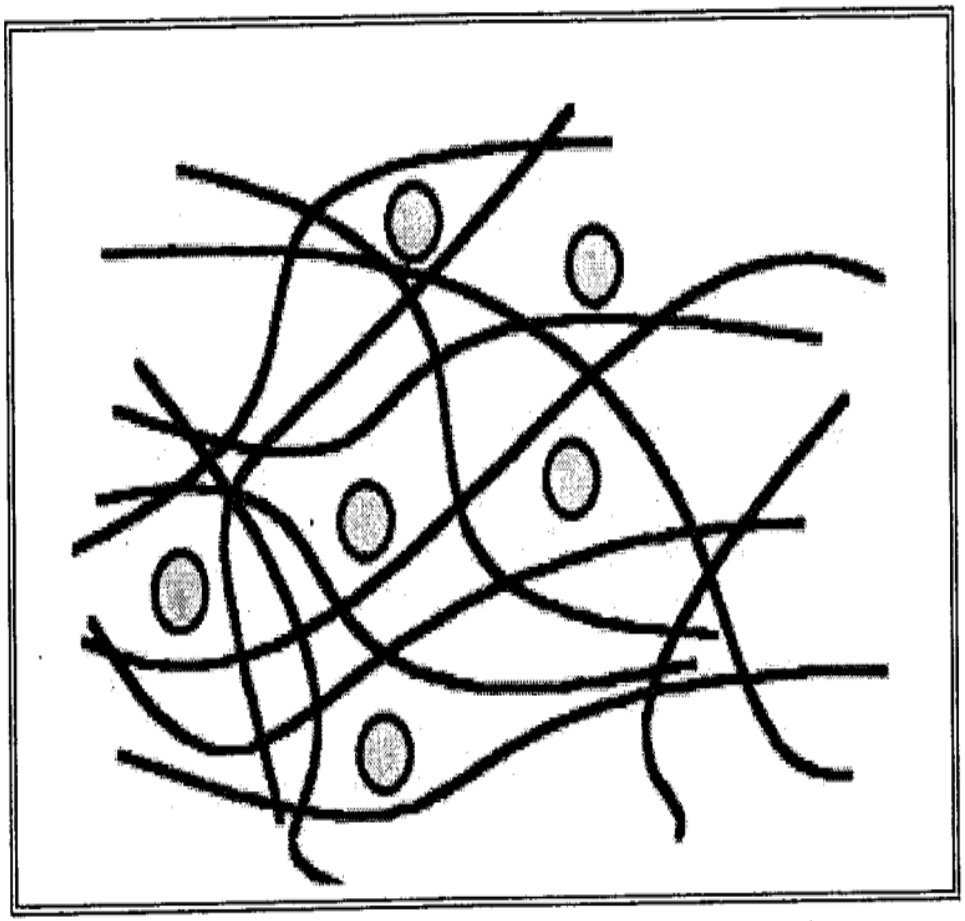
Permeability

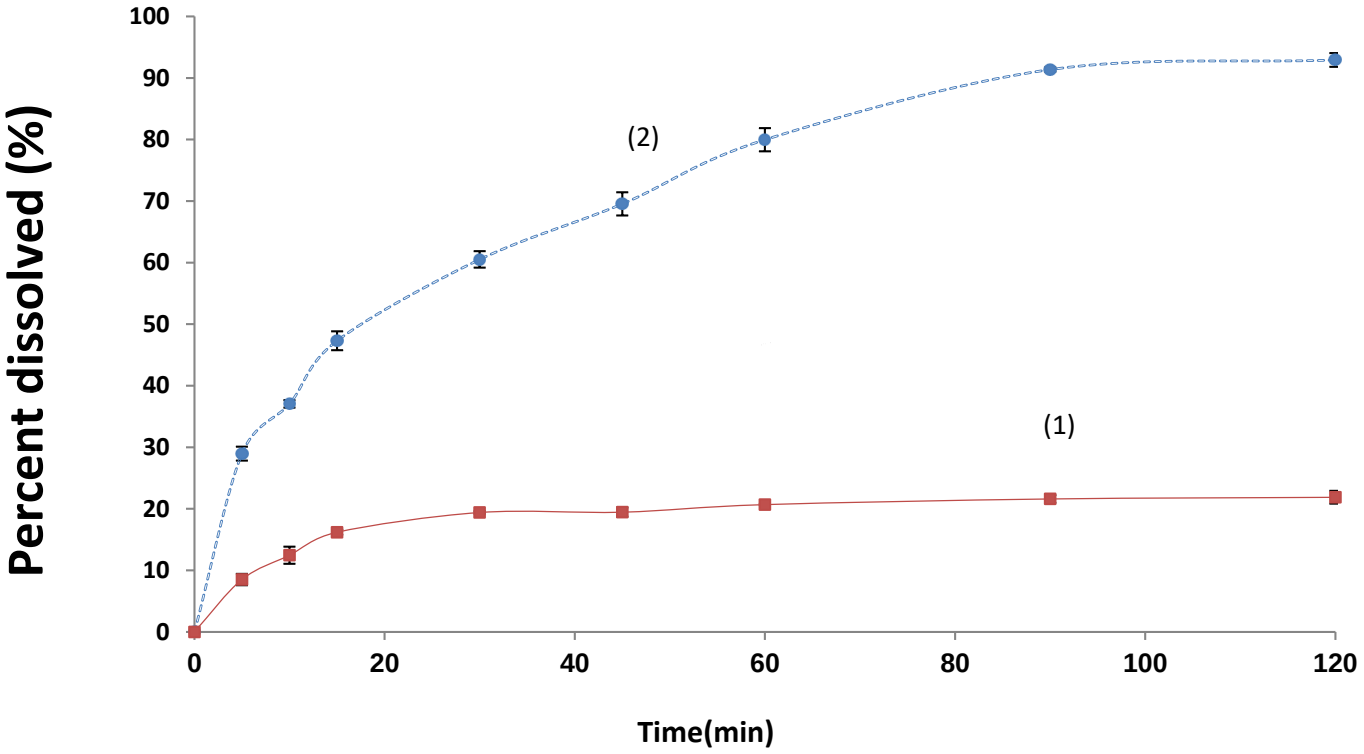


Enhancing dissolution profile
تحسين مرتسم الانحلال

المبعثرات الصلبة

solid dispersion



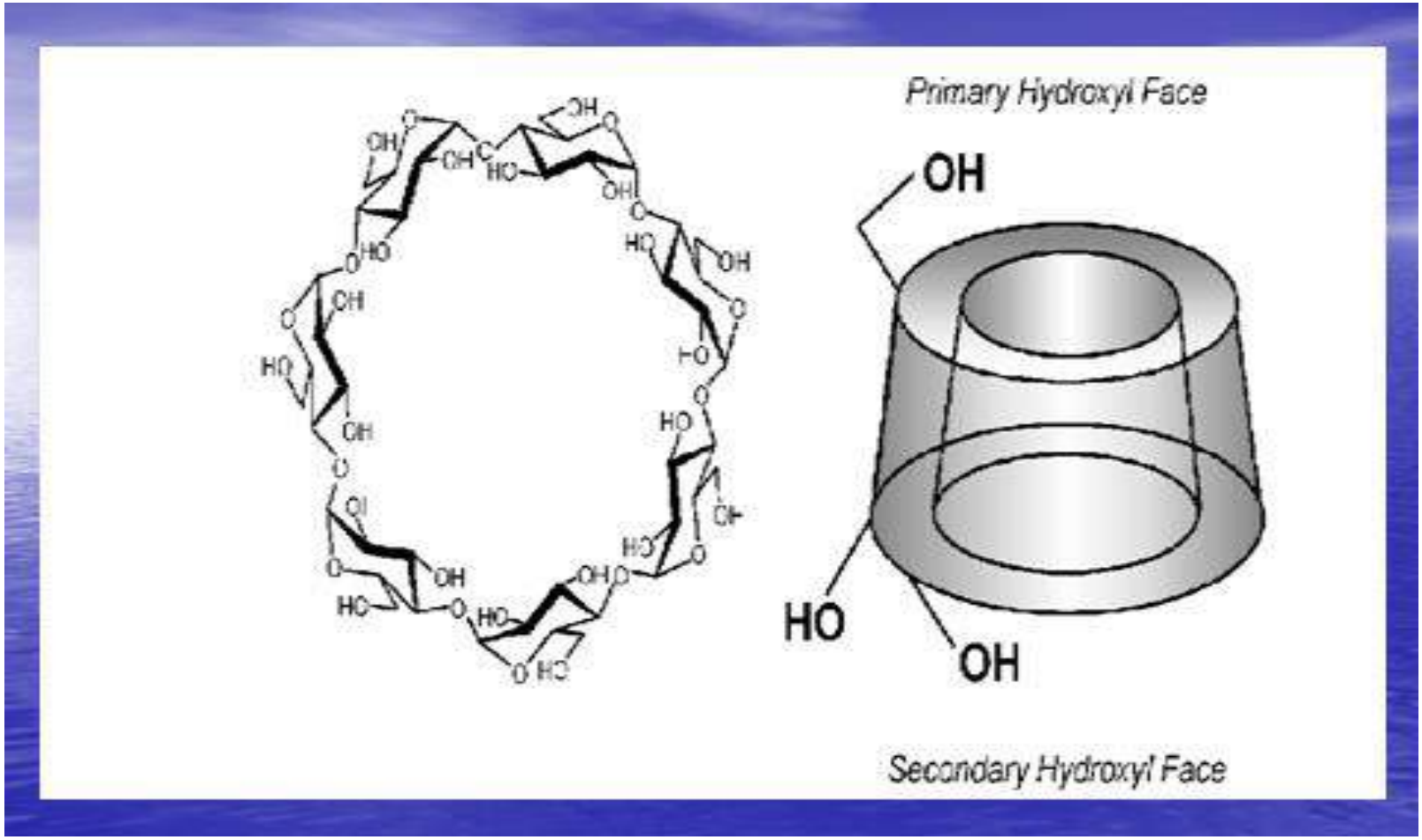


fig(12): percentage of nystatin released from tablets containing (1) nystatin plain powder, (2)nystatin :PEG6000 solid dispersion

K. Sakeer, H. Al-Zein, I. Hassn, G. P. Martin, and A. Nokhodachi. Pharmaceutical Development and Technology 2010,15(4) 360-368

تشكيل معقدات مع مشتقات السيكلوديكسترين

Complexation with cyclodextrin derivatives



تشكيل معقدات مع مشتقات السيكلوديكسترين

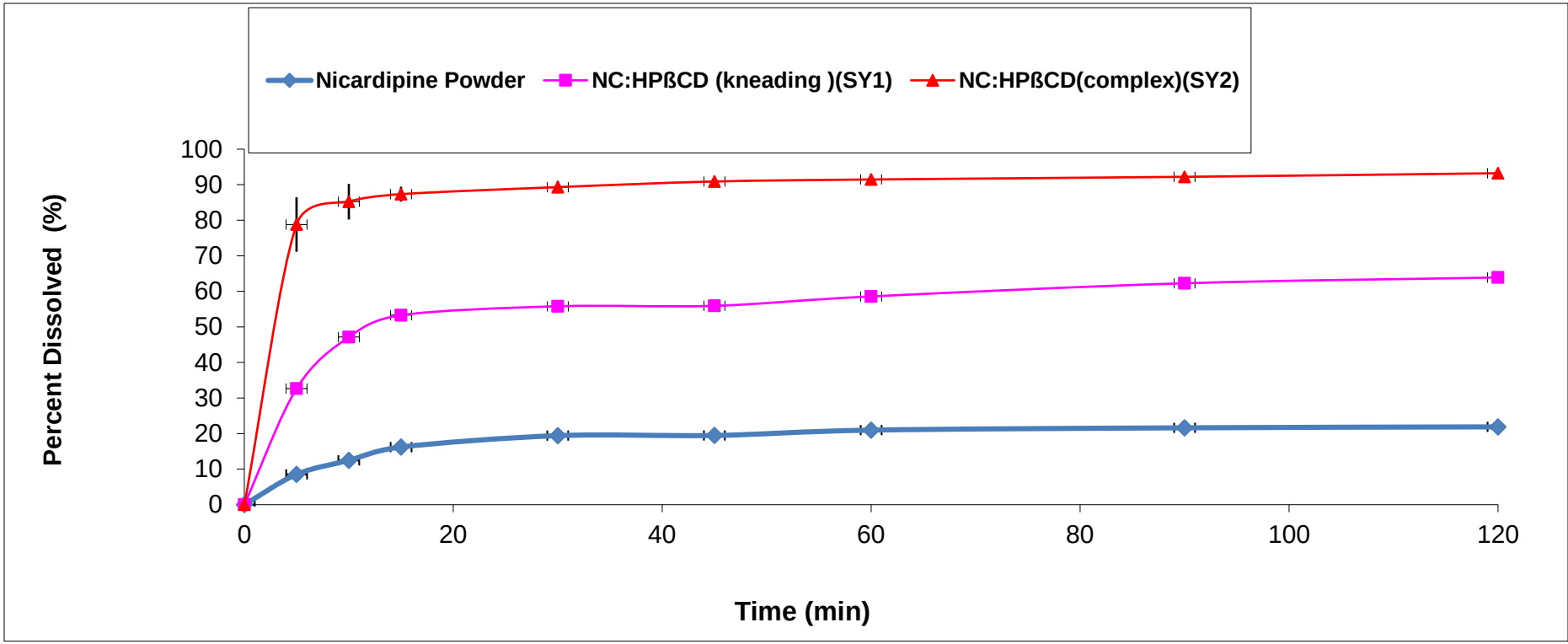


Figure (2): Percent dissolved of nicardipine as powder and inclusion complex with (HBβCD) prepared by kneading and rotatory evaporation in pH:6.8

H.Al-Zein et al, Saudi Pharmaceutical Journal 2011,19(4) ,245–253

النسبة المئوية المتحررة من الكانديزارتان سيلكسيتيل من أقراص :

- **المبعثرات الصلبة (SD1:4)**
- **المعقدات الانضمامية (IC1:1)**
- **الأنظمة السائلة الصلبة (LS) باستخدام محلول دوائي بتركيز (8%)**
- **المستحضر التجاري العالمي (Atacand®)**

IC1:1	SD1:4	LS	Atacand®	الزمن (دقيقة)
45.88±5.94%	49.74±4.91%	65.75±5.40%	16.46±3.18%	5
56.55±4.05%	65.47±3.55%	75.44±4.53%	27.30±2.55%	10
66.64±3.19%	78.37±3.10%	86.54±3.15%	48.54±2.30%	20
80.00±2.11%	83.91±2.33%	95.51±3.27%	68.98±1.97%	30
88.54±2.97%	91.98±1.57%	100.87±2.20%	86.80±0.50%	45
98.94±2.18%	98.60±0.81%	101.78±1.70%	99.94±2.18%	60

R. Al-Nus, H. El-Zein, Asian journal of Pharmaceutical and Clinical Research, vol 8, Issu 1, 2015.

تحسين معدل ذوبان الكانديسارتان

مرتسمات تحرر الكانديزارتان سيلكسيتيل من أقراص :

- **المبعثرات الصلبة (SD1:4)**
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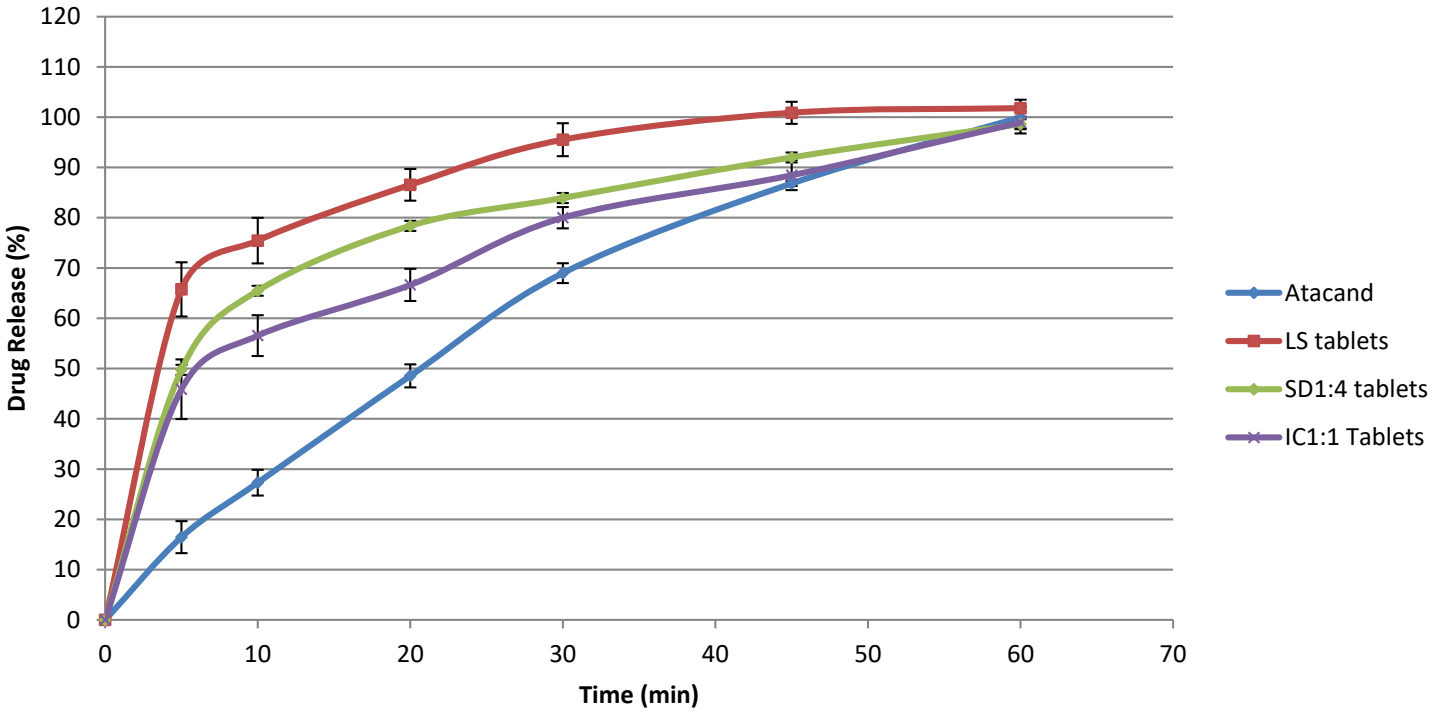


R. Al-Nus, H. El-Zein, Asian journal of Pharmaceutical and Clinical Research, vol 8, Issu 1, 2015.

BIOPHARMACEUTICS CLASSIFICATION SYSTEM

API	BCS	API	BCS	API	BCS
Alprazolam	Class I	Clarithromycin	LS	Nimesulide	Class II
Amlodipine	Class I	Doxazocin	Class I	Nitrofurantoin	Class IV
Ascorbic Acid	Class III	Flurbiprofen	Class II	Penicilamine	Class III
Atorvastatin	Class II	Folic Acid	Class IV*	Simvastatin	Class II
Azithromycin	LS - Class II	Glipizide	Class II*	Terazocin	Class III
Celecoxib	Class II	Ibuprofen	Class II	Terbinafine	Class I
Cetirizine	Class I	Montelukast	Class I	Valsartan	Class II
Levocetirizine	Class I	Lomefloxacin	Class I	Lidocaine	Class I
Minocycline	Class I	Niacin	Class III	Pravastatin sodium	Class I

الاعفاء الحيوي المستند الى التصنيف الصيدلاني الحيوي

BCS BASED BIOWAIVERS

BIOPHARMACEUTICS CLASSIFICATION SYSTEM (BCS)

- FDA Guidance for Industry: Immediate Release Solid Oral Dosage Forms: Scale-Up and Post-Approval Changes, November 1995.
- FDA Guidance for Industry: Waiver of In Vivo Bioavailability and Bioequivalence Studies for Immediate-Release Solid Oral Dosage Forms Based on a Bio pharmaceutics Classification System, FDA, August 2000.

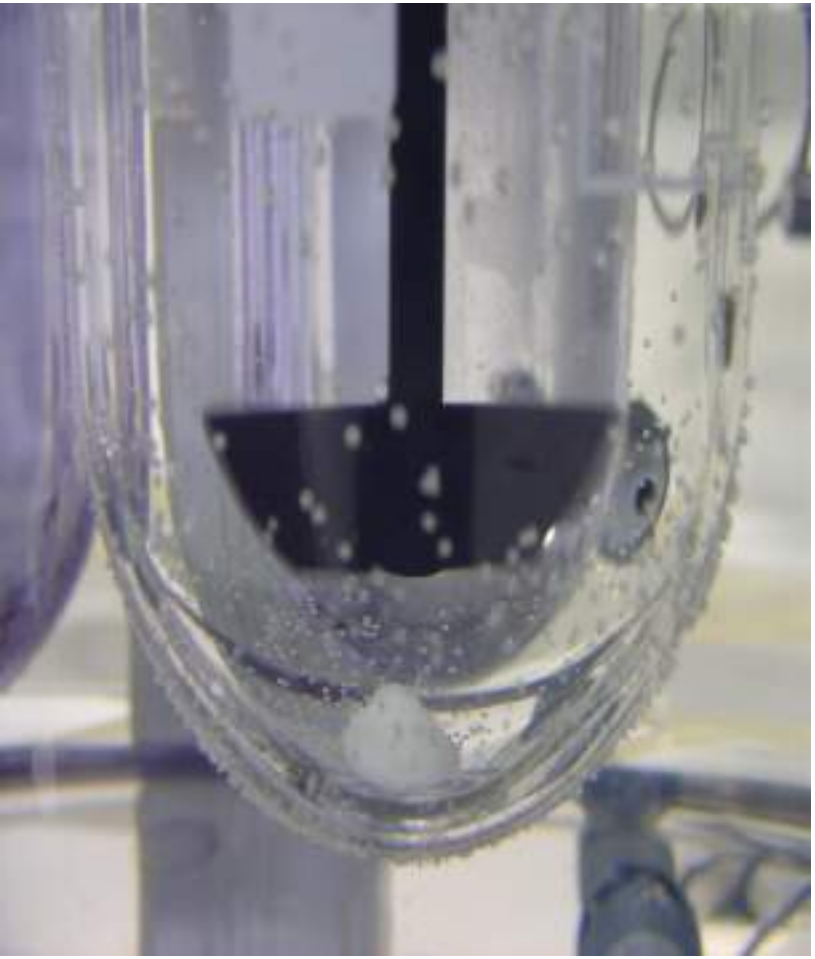
http://www.fda.gov/cder/guidance/cmc5.pdf
http://www.fda.gov/cder/guidance/3618fnl.pdf

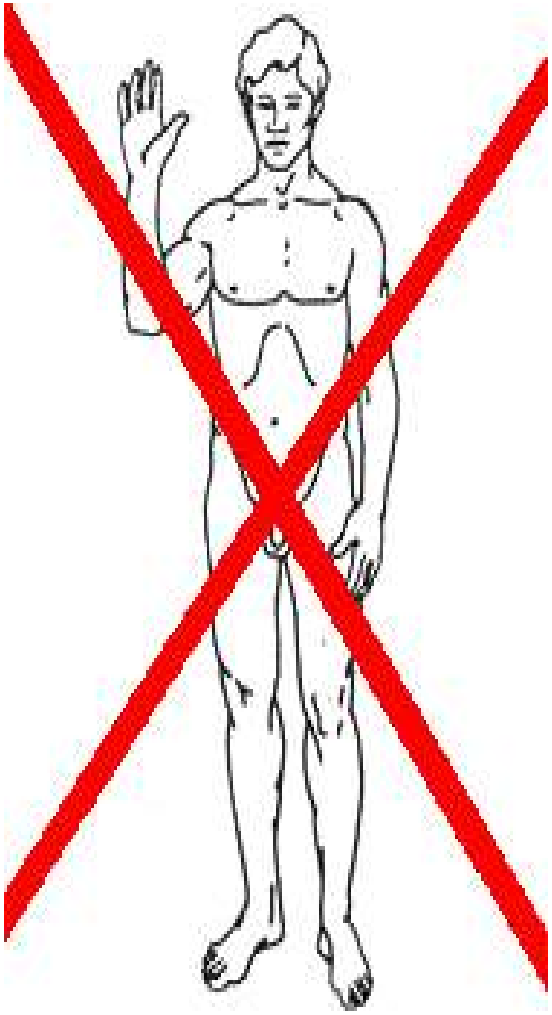
Biowaiver الاعفاء الحيوي

الاعفاء الحيوي هو قبول استبدال دراسات التكافؤ الحيوي في المختبر بالدراسات في الانسان.

Biowaiver is in vitro instead of *in vivo*
'bioequivalence' testing

الاعفاء الحيوي





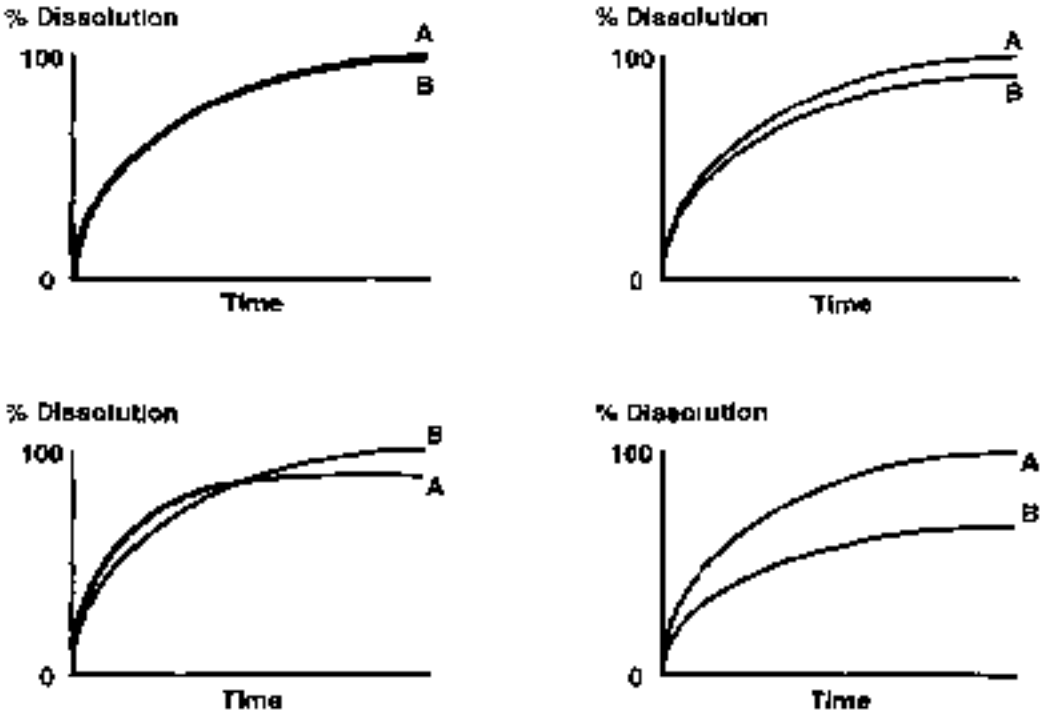
FDA BCS-BIOWAIVER GUIDANCE
Dissolution

- FDA criteria for BCS-based biowaiver:
  - **BCS class I** drug substances
  - Oral IR solid dosage form
  - Rapid in vitro dissolution and similar to **REFERENCE** product
  - Wide therapeutic window
  - Excipients should be FDA approved for IR solid dosage forms

مقارنة مرتسمات الانحلال

Dissolution Profile Comparison

Are These Profiles Similar?



USP Chapters <711>, <724>

USP apparatus

Apparatus 1	Rotating Basket	Capsules,Tablets
Apparatus 2	Paddle	Tablets, Capsules, modified drug products, suspensions
Apparatus 3	Reciprocating cylinder	Extended release drug products
Apparatus 4	Flow cell	Drug products containing low-water-soluble drugs
Apparatus 5	Paddle over disk	Transdermal drug products
Apparatus 6	Cylinder	Transdermal drug products
Apparatus 7	Reciprocating disk	Transdermal drug products
Diffusion Cells (Franz)	(Non-USP-NF)	Ointments, Creams, transdermal drug products

Similarity Factor عامل التشابه

$$f_2 = 50 \cdot \log \{[1 + (1/n)\Sigma_{t=1}^{n} (R_t - T_t)^2]^{-0.5} \cdot 100\}$$

n = عدد النقاط الزمنية

Rt= x النسبة المئوية الذائبة من المستحضر المرجعي عند النفطة الزمنية

Tt= x النسبة المئوية الذائبة من المستحضر المرجعي عند النفطة الزمنية

- ثلاث نقاط زمنية على الأقل
- 12 يجب العمل على 12 وحدة من المستحضرين
- قياس واحد فقط بعد الوصول الى 85% ذويان
- RSD:≤ 20% at early time point & ≤ 10% at higher time points

EMA BE GUIDELINE 2010
APPENDIX III BCS-BASED BIOWAIVER

European Medicines Agency

London, 20 January 2010
Doc. Ref.: CPMP/EWP/QWP/1401/98 Rev. 1/ Corr **

COMMITTEE FOR MEDICINAL PRODUCTS FOR HUMAN USE (CHMP)

GUIDELINE ON THE INVESTIGATION OF BIOEQUIVALENCE

http://www.ema.europa.eu/docs/en_GB/document_library/Scientific_guideline/2010/01/WC500070039.pdf

EMA BIOEQUIVALENCE GUIDELINE - 2010 solubility drug substance

- The pH-solubility profile of the drug substance should be determined and discussed.
- The drug substance is considered highly soluble if the ***highest single dose administered*** as immediate release formulation(s) is completely dissolved in 250 ml of buffers within the range of **pH 1 – 6.8** at 37 ± 1 °C.

  This demonstration requires the investigation in at least three buffers within this pH range (preferably at pH 1.2, 4.5 and 6.8)

EMA BIOEQUIVALENCE GUIDELINE - 2010
drug substance

- BCS-based biowaivers are applicable for IR drug products if:
  1. The drug substance has been proven to exhibit high solubility and complete absorption: **BCS-class I,**
  2. Either very rapid (>85% within 15 min) or similarly rapid (85% within 30 min) *in vitro dissolution characteristics of the test and* the reference product has been demonstrated considering specific requirements,
  3. Excipients that might affect bioavailability are qualitatively and quantitatively the same; in general the use of the same excipients in similar amounts is preferred.

EMA BIOEQUIVALENCE GUIDELINE - 2010
drug substance

- BCS-based biowaivers are also applicable for IR drug products if:

1. The drug substance has been proven to exhibit high solubility and limited absorption: **BCS-class III,**
2. Very rapid (>85% within 15 min) *in vitro dissolution* characteristics of the test and the reference product has been demonstrated considering specific requirements,
3. Excipients that might affect bioavailability are qualitatively and quantitatively the same and other excipients are qualitatively the same and quantitatively very similar.

WHO BIOWAVIER GUIDELINES

WHO Technical Report Series, No. 937, 2006

Annex 7

Multisource (generic) pharmaceutical products: guidelines on registration requirements to establish interchangeability

Annex 8

Proposal to waive in vivo bioequivalence requirements for *WHO Model List of Essential Medicines* immediate-release, solid oral dosage forms

http://healthtech.who.int/pq/info_general/documents/TRS937/WHO_TRS_937__annex7_eng.pdf

http://healthtech.who.int/pq/info_general/documents/TRS937/WHO_TRS_937__annex8_eng.pdf

BIOPHARMACEUTICS CLASSIFICATION SYSTEM (BCS)*

- BCS Class 1: HS/HP
  - VRD or RD in pH 1.2, 4.5 and 6.8
- BCS Class 2: LS/HP/Weak Acids
  - Rapid dissolution in pH 6.8 and similar dissolution profile in pH 1.2, 4.5 and 6.8
- BCS Class 3: HS/LP/VRD

For biowaivers Test (multisource) and Reference (comparator) products must have similar dissolution profile (f_2) in all 3 media

***Ref: WHO Technical Report Series, No. 937, 2006, Annex 7: Page: 347-390 and Annex 8: Page 391-438.**

EMA BE guideline - 2010

المقادير الجرعية المختلفة

يجرى التكافؤ الحيوي على أعلى جرعة اذا كانت حركية الدواء خطية على أن تتوافر الشروط التالية:

1- طريقة التحضيرواحدة

2- السواغات المستخدمة نفسها

3-يوجد تناسب كمي بين مكونات الصيغة

4- نتائج مرتسمات الانحلال متشابهة

MULTIPLE DOSE STRENGTHS
EMA BE guideline - 2010

- If several strengths of a test product are applied for, it may be sufficient to establish BE at only the highest strength,

.

- The strength(s) to evaluate depends on the linearity in pharmacokinetics of the active substance.

Comparative dissolution testing

Similarity factor f2

$$f_2 = 50 \cdot \log \{[1 + (1/n)\Sigma_{t=1}^{n} (R_t - T_t)^2]^{-0.5} \cdot 100\}$$

n = number of time points

Rt= % API dissolved of reference product at time point x

Tt= % API dissolved of test product at time point x

- Minimum of 3 time points (zero excluded)
- 12 units (one / vessel) for each batch (for "official" purposes)
- Only one measurement should be considered after the reference product has reached 85 % dissolution.
- RSD:≤ 20% at early time point & ≤ 10% at higher time points

Dissolution Profile Comparison

$$f_1 = \{[\Sigma_{t=1}^{n} | R_t - T_t |]/[\Sigma_{t=1}^{n} R_t]\} \bullet 100$$

$$f_2 = 50 \bullet \log \{[1+(1/n)\Sigma_{t=1}^{n} (R_t - T_t)^2]^{-0.5} \bullet 100\}$$

- R_t and T_t are the cumulative % dissolved at each of the selected n time points
- f_1 is proportional to the average difference between the two profiles (difference factor)
- f_2 is inversely proportional to the average squared difference between the two profiles and measures the closeness between the two profiles (similarity factor).

F1 between (0 – 15)

F2 between (50 – 100)

Comparative dissolution testing
Dissolution conditions (study design)

Apparatus (choice)	• USP 2 - Paddle, 50 (75) rpm **or** • USP 1 - Basket, 100 rpm
Dissolution media All three media for full comparison	1. Phosphate Buffer pH 6.8 or simulated intestinal fluid without enzymes 2. Acetate Buffer pH 4.5 3. 0.1 M HCl or buffer pH 1.2 or simulated gastric fluid without enzymes
Volume of media	900 ml or less
Temperature	37°C ± 0.5°C
Sampling points	10, 15, 20, 30, 45, (60, 120) min. (typical)
Units (individual)	12 for “official” studies

Example

Ciprofloxacin: two batches of same product

Product	Manufacturer	Batch Nr	Expiry date	Status
Cipro 500	ABC Ltd	xxx	06/2007	Test
Cipro 500	ABC Ltd	zzz	07/2007	Reference

Apparatus paddle at 50 rpm
Medium 1: simulated gastric fluid without pepsin (SGF) (900 ml)
Medium 2: acetate buffer pH 4.5 (900 ml)
Medium 3: phosphate buffer pH 6.8 (900 ml)
Temp.: 37°C ± 0.5°C (start, middle, end)
Units: Twelve tablets per medium, each batch
Sampling: Manual, through in-line filter (0.45 µm PVDF unit)
at 10, 15, 20, 30 and 45 minutes
Analysis: HPLC analysis for ciprofloxacin

Example .Cont….

Ciprofloxacin: two batches of same product

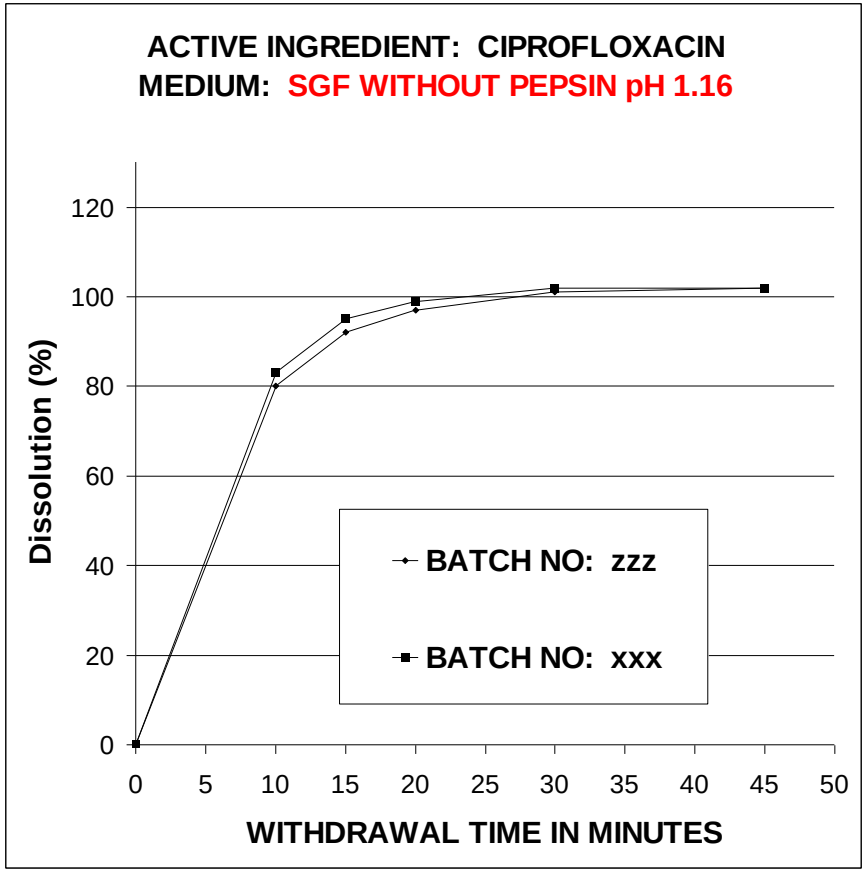
Medium ▶	SGF, pH 1.16		Buffer pH 4.5		Buffer pH 6.8	
	% dissolved		% dissolved		% dissolved	
Time (min)	b/n xxx	b/n zzz	b/n xxx	b/n zzz	b/n xxx	b/n zzz
10	83	80	93	96	28	31
15	95	92	97	99	34	36
20	99	97	99	100	38	39
30	102	101	100	100	39	40
45	102	102	102	101	39	41
similarity ? n = ?						

Conclusion: The profiles in all three media can be regarded similar / not similar.

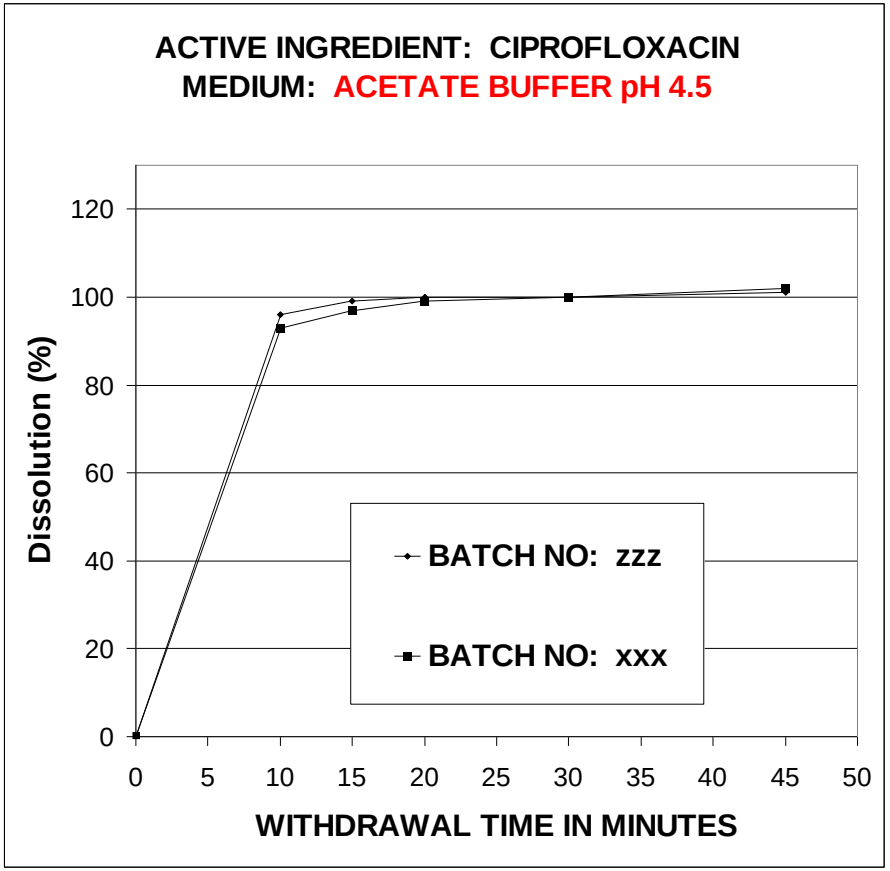
Example .Cont….

Ciprofloxacin: two batches of same product

SGF without pepsin, pH 1.16



Acetate buffer pH 4.5



Example .Cont….

Ciprofloxacin: two batches of same product

Phosphate buffer pH 6.8