

Application and Experience in the EU of the BCS Concept in the review of new generics & variations



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CONTENT OF PRESENTATION

- The EU system
- EU before and after the new NfG BA/BE
- Practice in the current EU:
 - ibuprofen
 - carbamazepine
- Sources of solubility & permeability data



The EU system



Th EU system

- **EU # FDA !!!!**
- **within EU: identical regulations (NfG)**
- **but NfG leaves freedom for interpretation:**
 - “normally.....“
 - “in exceptional cases.....”
 - “not for narrow therapeutic drugs.....”



The EU system

- “EU” assessment by a mixed system:
 - **central EMEA procedure**
 - biotech drugs & high-tech drug
 - not relevant for biowaiving
 - **national assessment**
 - no-high tech, national drugs
 - no assessments available!
 - **mutual recognition**
 - not high-tech national drugs
 - only source of biowaiving experience



- NfG`s valid over whole EU



- But actual practice in Ireland???



The EU system



- Companies will not go MR with drugs with insufficient files
- EU countries re-review drugs before going



EU before and after the new NfG BA/BE



EU before and after the new NfG BA/BE

- **Before the new NfG BA/BE:**

- **Lists:**

Germany:

Gleiter et al, J Clin Pharmacol 1998, 904-911.

When are Bioavailability studies required?

Drug substances for which BA Studies are not generally required:

hydrochlorthiazide captopril cimetidine

ibuprofen ketotifen etc.

piroxicam oxazepam etc.



EU before and after the new NfG BA/BE

- NI also “positive list”
- most: ”assessors gutfeeling”



EU before and after the new NfG BA/BE

- **After the new NfG BA/BE:**
 - formally:
 - proof of no need for BE-study (= biowaiving, as per BCS) to be done by MA-applicant
- variation Type I, nr. 18 Replacement of an excipient with a comparable excipient: Comparative dissolution profiles..of old and new composition
Justification for not submitting a new bioequivalence study according to the current *NfG on BA/BE*.



EU before and after the new NfG BA/BE

- **After the new NfG BA/BE:**
- **on MR-level:**
 - new MA`s:
one MA granted with biowaiving
 - variations on existing MAS`s:
more biowaivers
for small changes

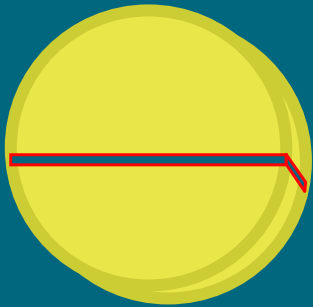


Practice in the current EU: ibuprofen carbamazepine

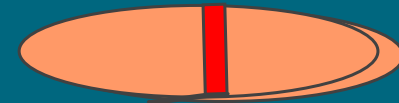


Ibuprofen IR tablet

New MA
=
new generic



Test



Reference



Ibuprofen IR tablet

- **permeability of ibuprofen**
- Potthast et al, in preparation:
 - ibuprofen is rapidly and completely absorbed, indicating high permeability....
 - A high Caco-2 permeability also indicates a high permeability...



Ibuprofen IR tablet

- **solubility of ibuprofen**

at 37 °C in mg/ml

☒ pH 1	0.04	outside BCS-limit for Class II!
☒ pH 3	0.04	outside BCS-limit for Class II!
☒ pH 4,5	0.08	outside BCS-limit for Class II!
pH 5,5	0.69	
pH 6,8	3.37	
pH 7,4	3.44	

Potthast; 2002



Ibuprofen IR tablet

- **Ibuprofen is Class II BCS**
- **in MR procedure for new MA:**
- **BE study will be required!**

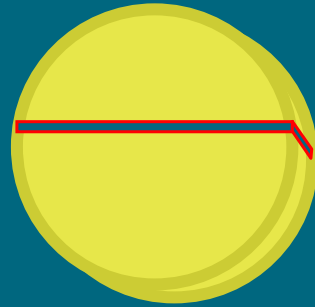


Ibuprofen IR tablet

- **But for a variation within a existing product:**



Ibuprofen IR tablet



New

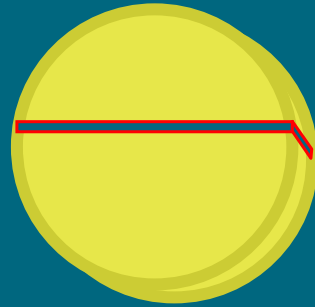


Old

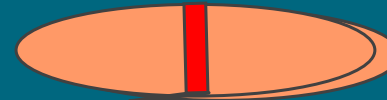
Comparitive quantitative excipient listing !



Ibuprofen IR tablet



New



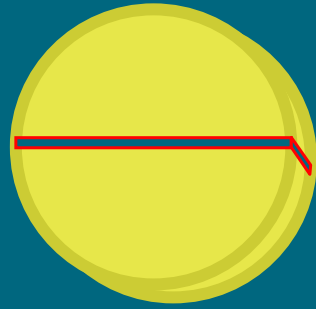
Old

ferric oxide yellow	a mg
lactose monohyd	b mg
magnesium stearate	c mg
maize starch	d mg
Na starch glycolate	e mg

ferric oxide red	a mg
lactose monohydrate	z mg
magnesium stearate	c mg
potato starch	d mg
Na starch glycolate	e mg



Ibuprofen IR tablet



Test



Reference

Also:

Ibuprofen in test and reference:

- same polymorphic form
- same particle size
- same AIM



Ibuprofen IR tablet

also:

- Ibuprofen is one of the safest NSAIDs available on the market
- wide therapeutic window
 - Martindale



Ibuprofen IR tablet

- **BCS allows no biowaiving**
- **but gap to be bridged is very small**
- **no big risks**
- **within-product a biowaiver was accepted by EU authorities**



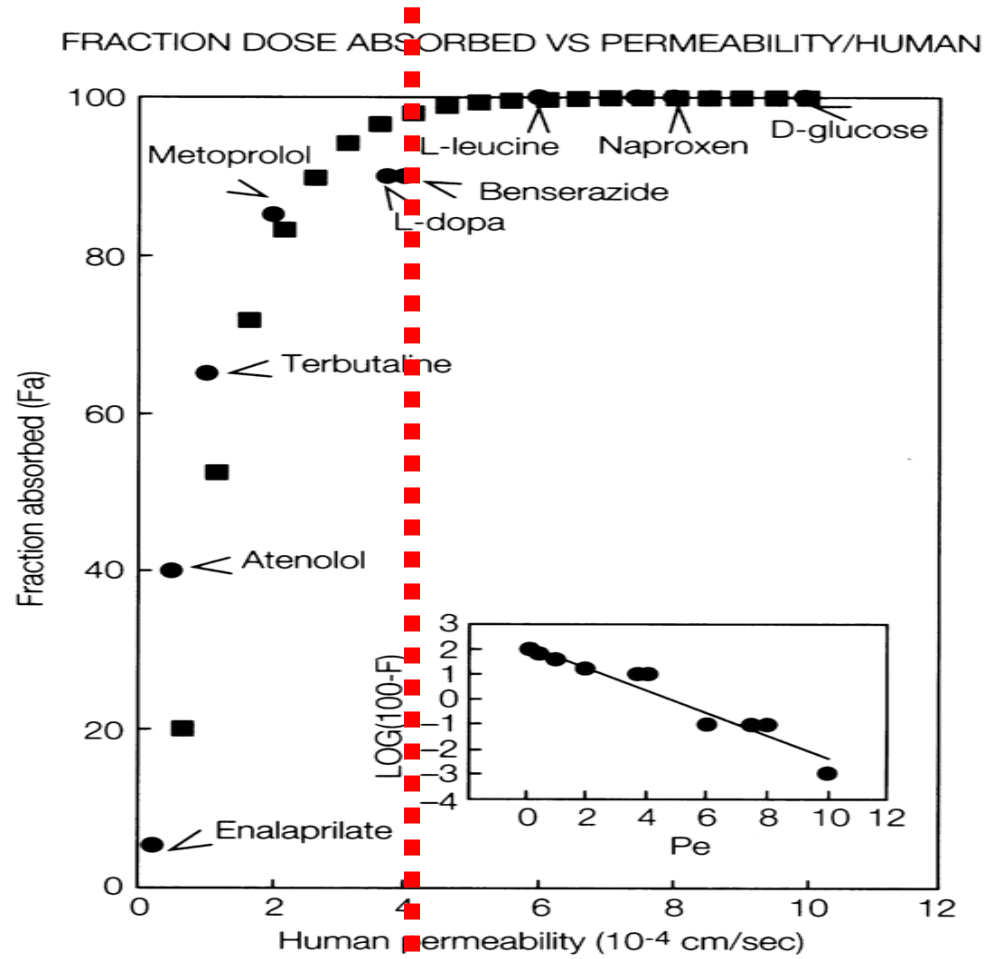
carbamazepine

Solubility:

- Insoluble in water
- No acidic groups, no basic groups
- **Permeability:**
 - Absorption $\approx 100\%$
 - Perm. human intestinal: $4 \cdot 10^{-6} \text{ m}\cdot\text{sec}^{-1}$



carbamazepine



carbamazepine

- **BCS Class II**
 - IVIVC to be expected

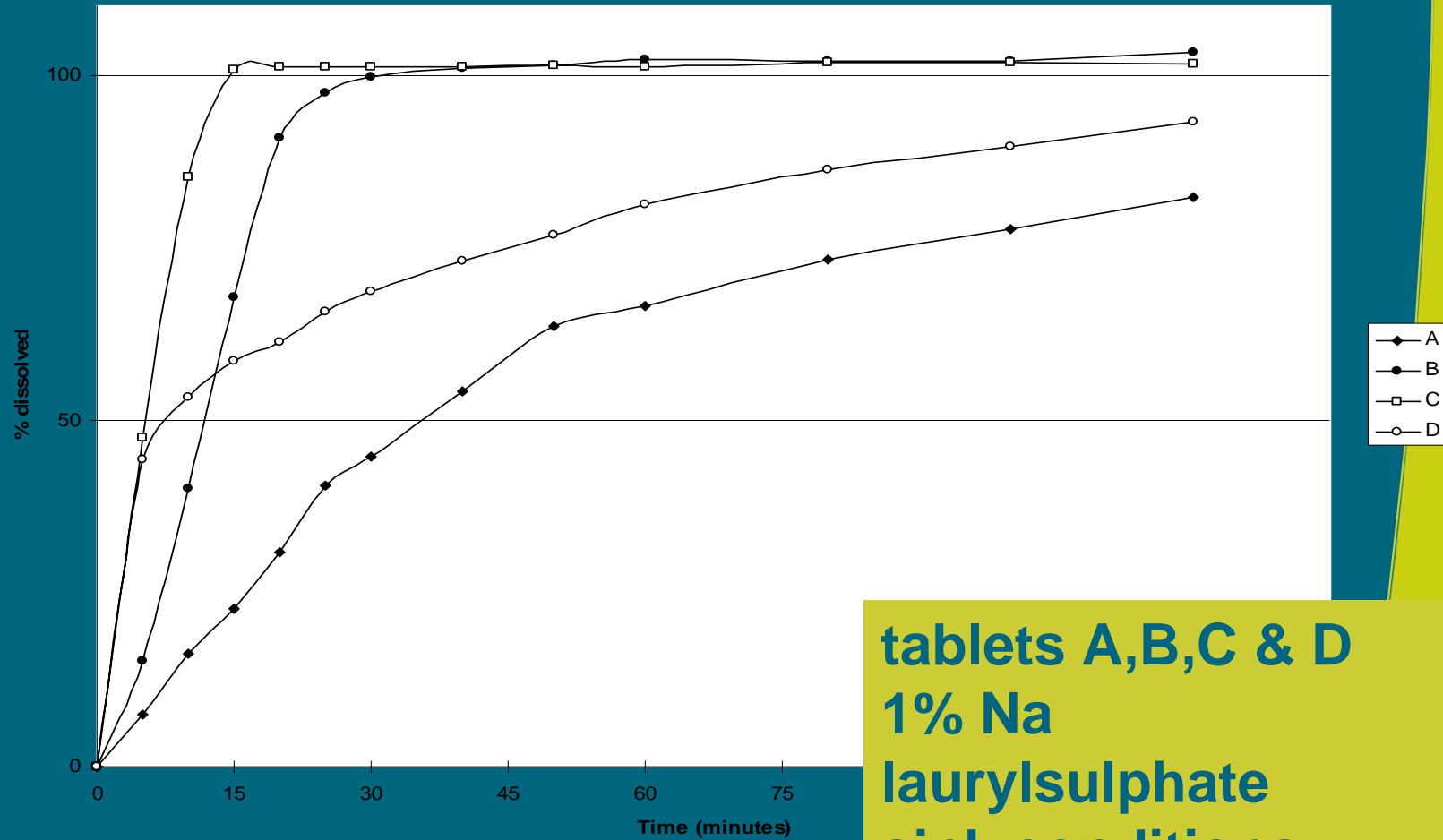


carbamazepine

- Lake, Olling & Barends, Eur J Pharm Biopharm 1999: IVIVC level C
- Four IR tablets (A, B, C, D)
 - dissolution *in-vitro*
 - and
 - BE *in-vivo*



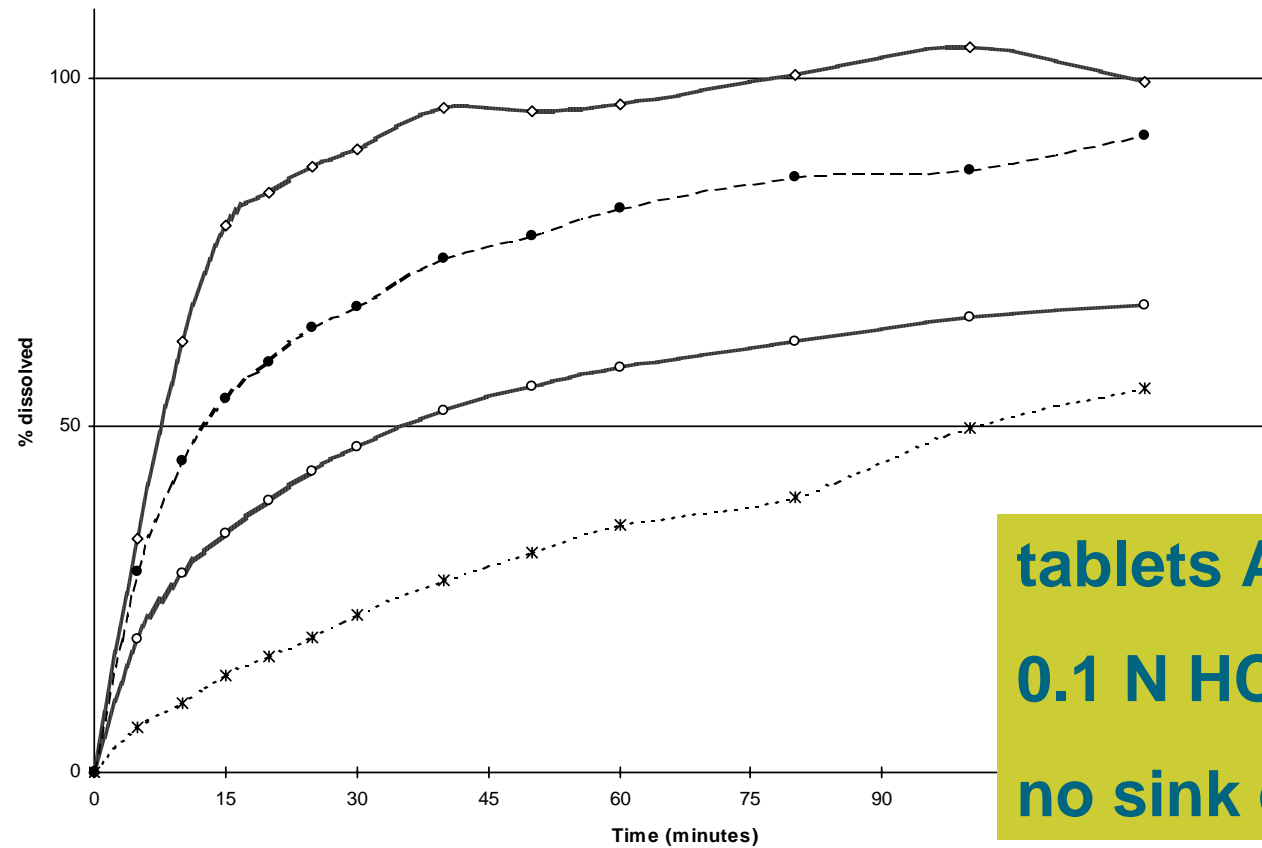
carbamazepine



tablets A,B,C & D
1% Na
laurylsulphate
sink conditions



carbamazepine



tablets A,B,C & D
0.1 N HCl
no sink conditions!



carbamazepine

Tablet	AUC ₀₋ mg/l	Cmax mg.h/l
A	246	3.3
B	294	5.9
C	292	6.2
D	296	4.5



carbamazepine

- **AUC invariant**
- **excellent IVIVC's for C_{max} demonstrated**



carbamazepine

- **BUT:**
- EU authorities will hardly accept biowaiver for carbamazepine based on IVIVC
- **BECAUSE:**
- critical drug
- know reports of BA failures



- **SO:**
- **BCS has its limitations**
- **but is a good starting point**



Sources of solubility & permeability data



Sources of solubility & permeability data

- Existing **solubility data** are not well suited to BCS needs
- **Permeability data:**
 - Caco-2 data are not very convincing
 - look for absolute BA!!!
 - >90% absolute BA = highly permeable
 - BA can be found in SmPC`s



Sources of solubility & permeability data

- **BCS-Classifications of WHO Essential drugs:**
- Kasim NA et al. Molecular Properties of WHO Essential Drugs and Provisional Biopharmaceutical Classification. Mol Pharm 2004; 1 85 - 96.
- Dressman JB et al. Classification of orally administered drugs on the WHO model list of essential medicines according to the biopharmaceutical classification system (BCS). Eur J Pharm Biopharm July 2004.



Sources of solubility & permeability data

- **Monographs pro active substance:**
- FIP WG on BA/BE, data mining project
- see www.fip.org → science → BA/BE; hyperlink to Newsletter



Sources of solubility & permeability data

- **Monographs pro active substance:**
- Vogelpoel H et al. Atenolol BCS monograph based on literature data. J Pharm Sci. Accepted for publication.
- Vogelpoel H et al. Propranolol HCl BCS monograph based on literature data. J Pharm Sci. Accepted for publication.
- Vogelpoel H et al. Verapamil BCS monograph based on literature data. J Pharm Sci. Accepted for publication.



Sources of solubility & permeability data

- **Monographs pro active substance:**
- monographs in progress:
 - ibuprofen
 - nifedipine
 - chloroquine
 - sotalol
 -
- **More contributions welcomed!**



**Thank you for
your attention!**

