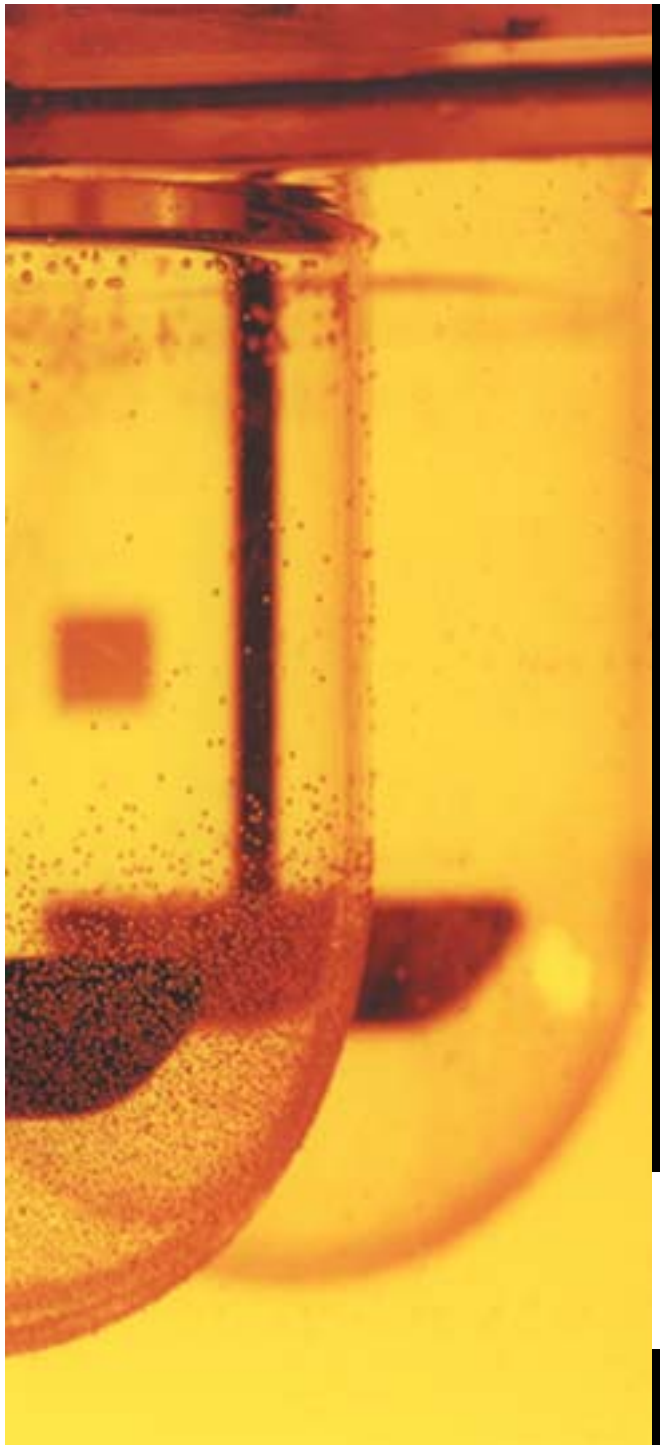


Bioavailability and Bioequivalence

IKEV / APV Conference Istanbul April 15-16, 2004

Quality of Clinical Trial Material to be Tested in Man

Dr. Johannes Krämer

PHAST Pharmaceutical Quality Standards

Topics

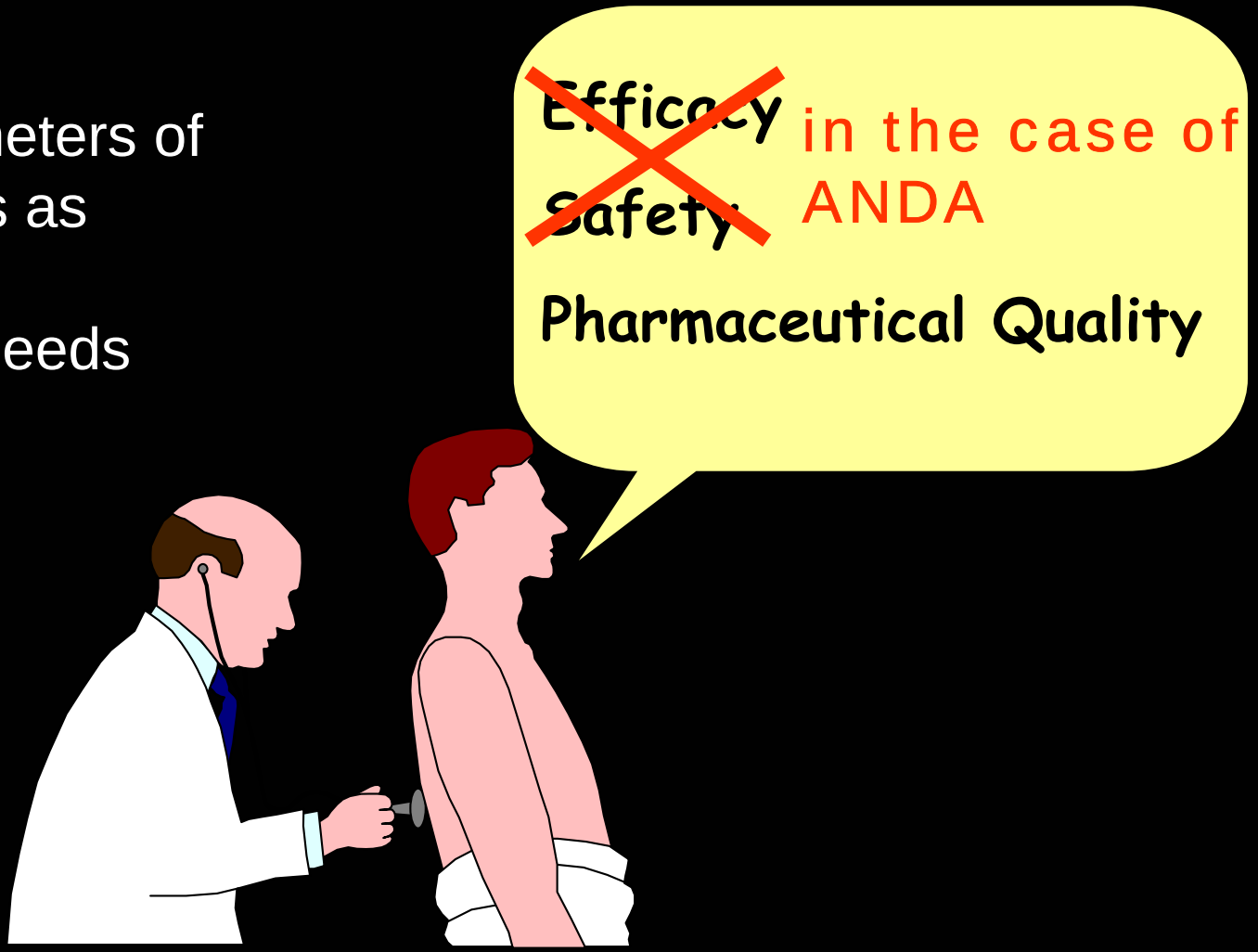
- The parameters of pharmaceutical quality
- Requirement for clinical phases I and II
- Special regard on reference product after blinding and repackaging

What Role Plays Dissolution Testing in Pharmaceutical Quality Control

- what is quality in general
- not only related to marketed products...
- ...but also to development pharmaceuticals
- not once but permanently during all steps of one products lifecycle
- dissolution testing can be/is the link between pharmaceutical analysis and clinical research

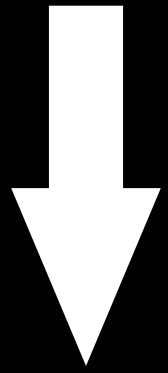
Regulatory Concern

Quality Parameters of Drug Products as Defined by Therapeutic Needs



Quality Investigations of Drug Products: New Drug Product

- **In Drug Development**
- **During the Manufacturing Process**
- **At the Time of Release**
- **At the End of Shelf-Life**
  - *–by sensoric*
  - *–chemical and/or biological*
  - *–physical*
  - ***–physicochemical techniques***



Problem: "Reproducibility of Quality"

within one lot → **intra-lot homogeneity**

within one product → **lot-to-lot conformity**

therefore, **G**ood **M**anufacturing **P**ractice

required by ANNEX 13 “Manufacture of investigational medicinal products JULY 2003”

"Definition of Quality by Setting of Specifications"

Why

- variation of starting materials
- variation of manufacturing process
- variation of product

Goal

- to assure intralot homogeneity and lot-to-lot consistency
- all batches / tablets are representative for the product
- not only investigational new product but also comparator

Quality Parameters of Solid Drug Products

Investigated in accordance with the product specification file

- **Pharmaceutical Quality**
  - purity "related substances"
  - content
  - uniformity of content
  - hardness
  - friability
  - identity
  - disintegration

Biopharmaceutical Quality

– dissolution

QP responsible for batch release

Setting Specifications: Content and Uniformity of Dose

Content

- US - 10 % (shelf-life)
- EU ± 5 % (shelf-life)

Uniformity of Dose

as uniformity of content

- EP: content ≤ 2 mg / 2 % of total mass
- USP: content ≤ 50 mg

as uniformity of mass

- EP: ± 15 % (average)
- USP: ± 15 % (label claim) and CV ≤ 6 %

• with regard to dose correction

Setting of Specifications Depending on Methods / Content and Uniformity of Dose

Content

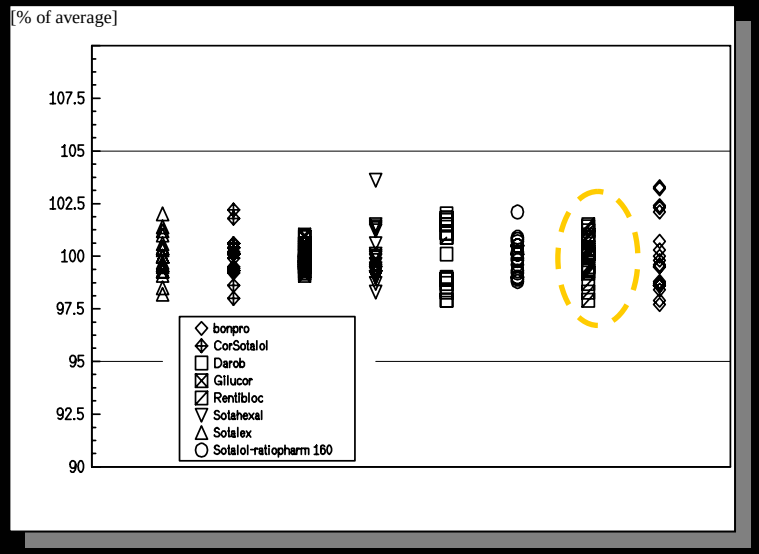
- by chemical analysis

Uniformity of Dose

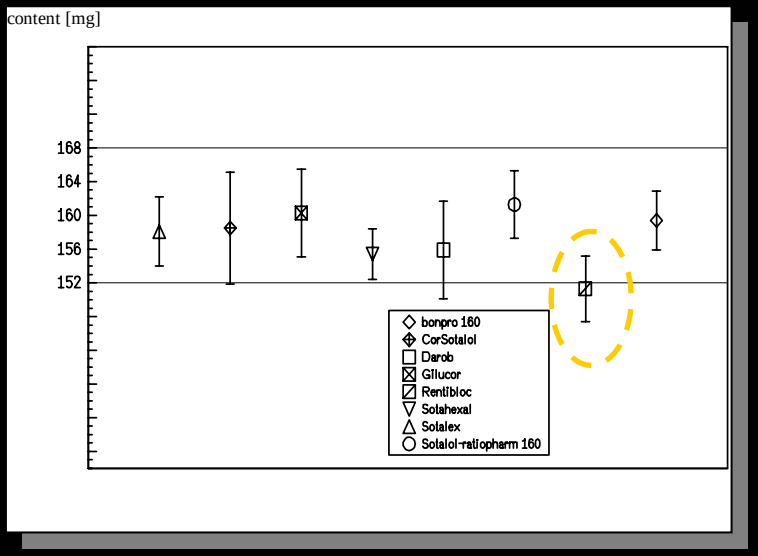
- as uniformity of content
  - by chemical analysis
- as uniformity of mass?
  - by weighing
    - » fast and precise
    - » not destructive
    - » fully automated
    - » ideal in IPC

Specifications: Uniformity of Dose
A Comparison of Methods

EU: uniformity of weight

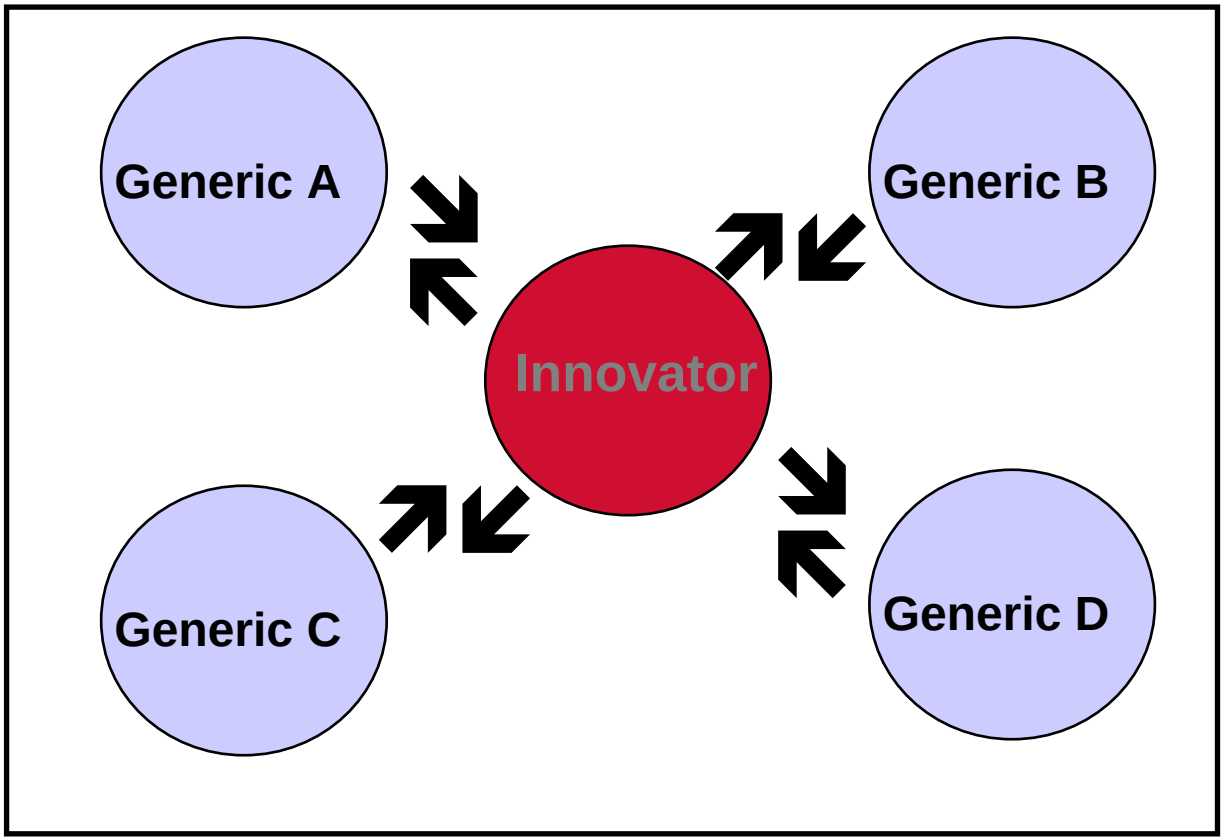


US: uniformity of content



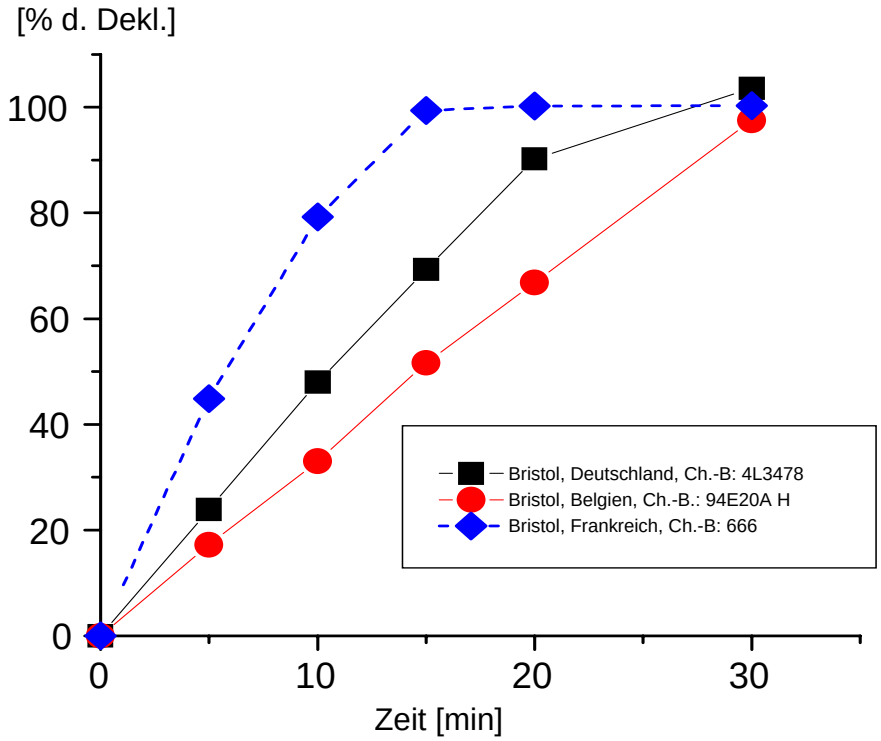
left and right identical samples

Choice of Reference Product / Comparator



Registered Brand in Different EU-Member States

Example Sotalex (160 mg sotalol hydrochlorid)



Blattrüher (DAB 1996), 100 U/min, 900 ml 0,1 N-HCl, 37 °C

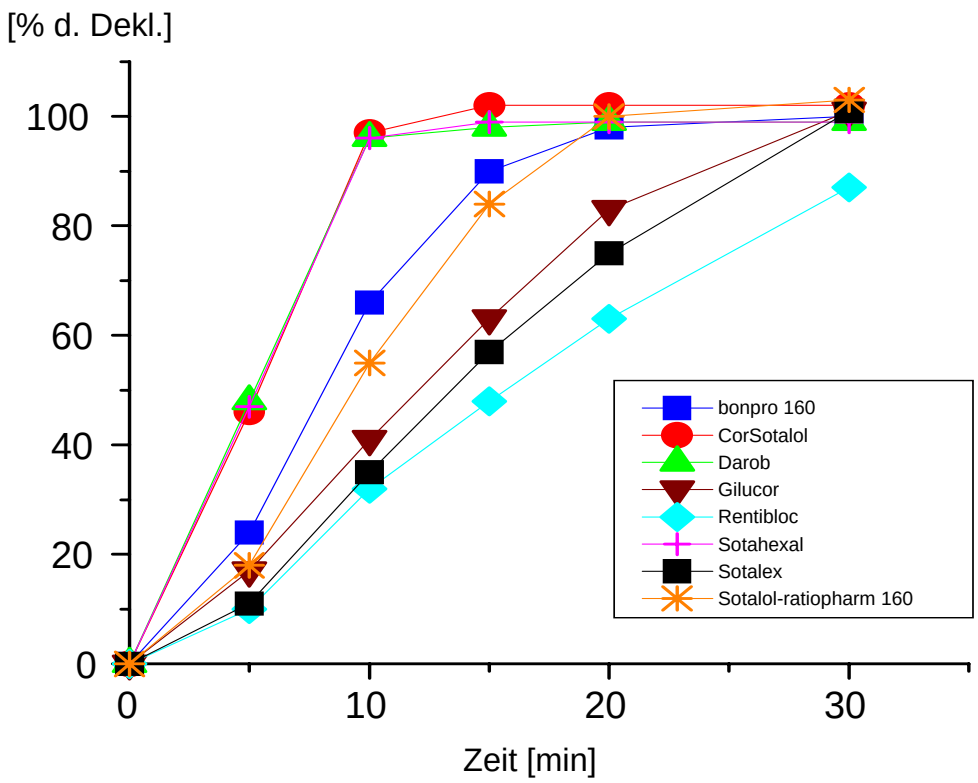
Innovator EU

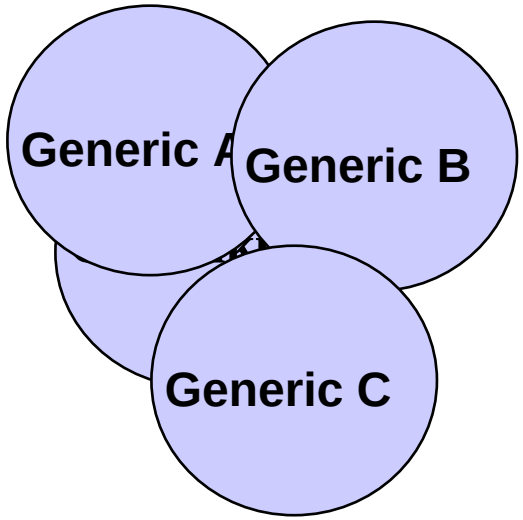
Biopharmaceutical differences:

- **Belgium**
- **Germany**
- **France**

German Generic vs. Registered EU-Brands

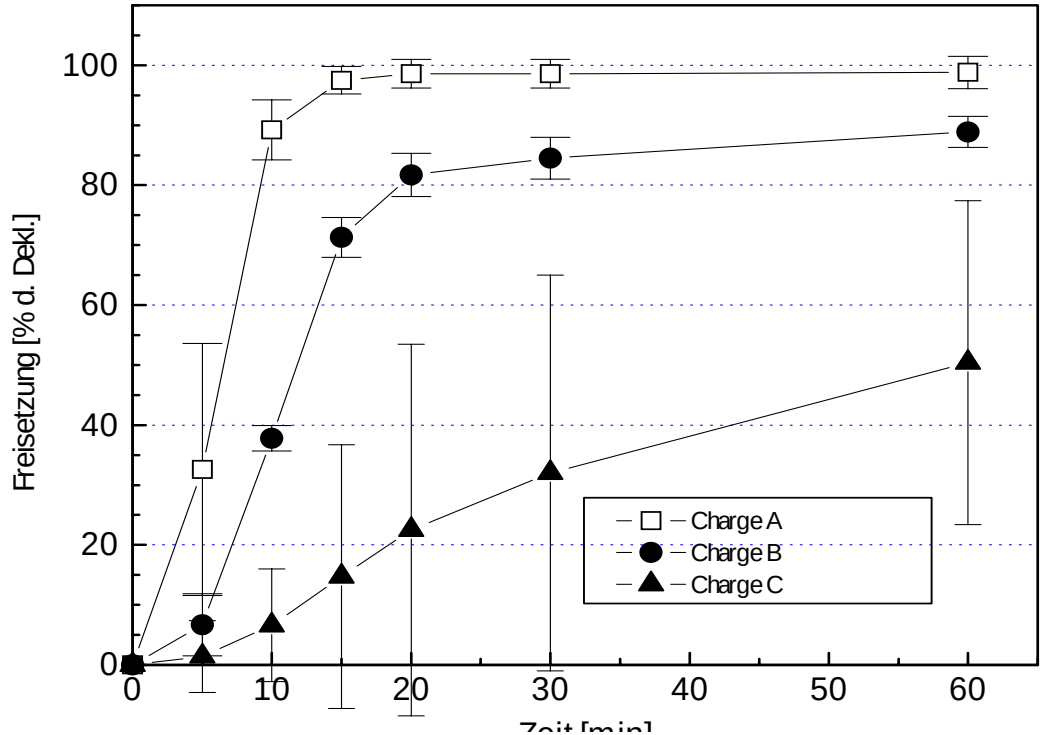
160 mg Sotalol hydrochlorid generic brands





Investigations on Lot-to-lot Conformity

chlorprothixene 15 mg sugarcoated tablets



basket, 100 rpm, 900 ml 0,1 N-HCl, 37 °C

Comparator Product

An investigational or marketed product (i.e. active control), or placebo, used as a reference in a clinical trial

- double blinded clinical studies
- blinded placebo provided by competitor
- commercial product blinded by:
  - over-encapsulation
  - film-coating
  - repackaging
  - wiping off printed inscriptions

Method Development

Sources of information

- compendia
- FDA freedom of information act
  - very little analytical information
  - dissolution method?
  - solubility
- published literature
- experience with similar products

Analytical Issues

barrier to dissolution

- capsule shell
  - –gelatin cross-linking
- filler may delay disintegration of encapsulated tablet

two tiered dissolution testing

Analytical Approach

- development for tablet alone
- testing of encapsulated product under same conditions
- compare for similarity
- perform linearity, precision, and filter checks to validate method

Comparison

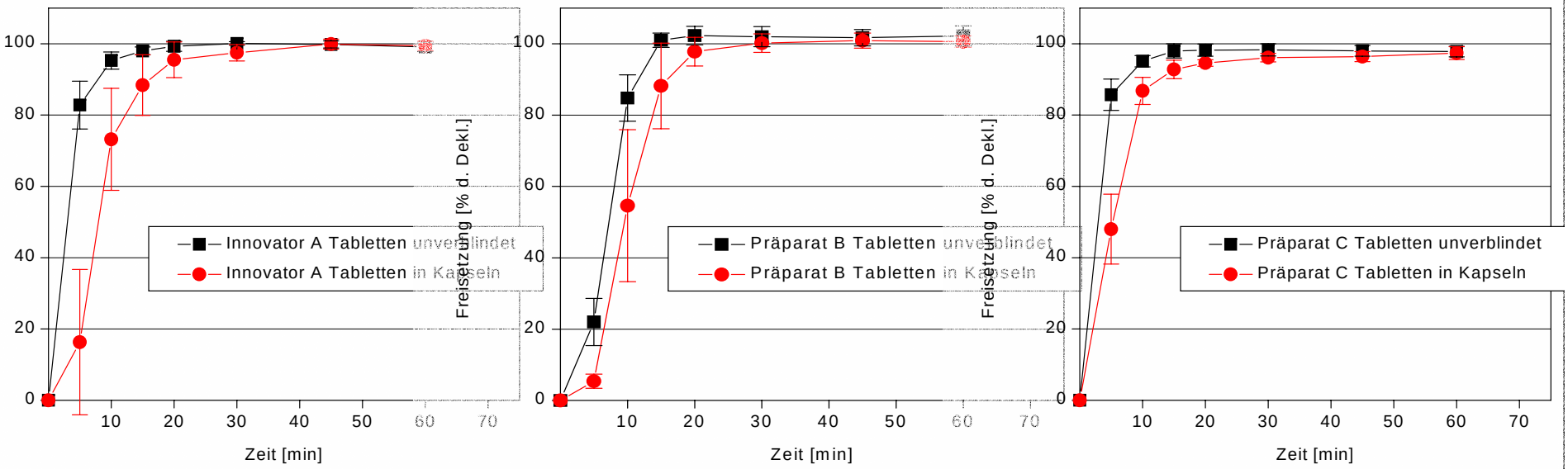
f_2 similarity factor

- used in comparison to data from other reference products
- SUPAC IR / MR and BCS guidances define and describe the use of f_2
- CPMP/QWP/1401/98 mentions f_2

Method Validation

- method will not need to be transferred to manufacturing site
- limited validation may suffice
  - filler / capsule interference
  - linearity
  - accuracy / precision (on actual sample) including a fast stir
  - filter check, deaeration, solution stability
- all validation can be done using the original drug product if no reference standard available

Example: Encapsulation of Different Products



paddle, 50 rpm, 900 ml simulated gastric fluid without enzyme

Example: Poor Chemical Stability after Repackaging

e.g.: degradation of comparator
(25°C / 60% r.F.)

time [months]	0	6	12	15
assay 10mg [%]	101	99	92	88
assay 20mg [%]	101	99	92	87

XYZ tablets with lactose in capsules
primary package: PE-multi-dose containers

Conclusions

- quality is closely related to efficacy and safety
- once defined for a model the major problem is reproducibility of quality of a real marketed product
- appropriate quality control methods and tools are required
- the analyst may rely in analytical results if methodology is properly validated and instruments are qualified and calibrated
- dissolution testing is most important tool