Overview of Dissolution for BA/BE

- **Biopharmaceutics Classification System based on Solubility/Permeability**
- Biowaivers for BCS I Drugs
- Discussion of BCS III Drugs
- Models establishing *in vivo-in vitro* Correlations (IVIVC Levels A-C)

next Lecture

Overview of Dissolution for BA/BE

- **Biopharmaceutics Classification System based on Solubility/Permeability**
  - **Class I** Solubility ↑ Permeabilty ↑
  - **Class II** Solubility ↓ Permeabilty ↑
  - **Class III** Solubility ↑ Permeabilty ↓
  - **Class IV** Solubility ↓ Permeabilty ↓

Amidon, G.L., Lennernäs, H., Shah, V.P. and J. R. Crison;
A theoretical basis for a biopharmaceutics drug classification: The correlation of in vitro drug product dissolution and in vivo bioavailability.
Pharm. Res. 12(3), 413-420 (1995)

next Lecture

Overview of Dissolution for BA/BE

- **Biopharmaceutics Classification System based on Solubility/Permeability**
  - Dissolution rate has a negligible impact on bio-availability of highly soluble and highly perme-able (BCS Class I) drugs when their formula-tion's dissolution is sufficiently rapid.

Kaus, L.C., Gillespie, W.R., Hussain, A.S. and G.L. Amidon;
The effect of in vivo dissolution, gastric emptying rate, and intestinal transit time on the peak concentration and area-under-the-curve of drugs with diffe-rent gastrointestinal permeabilities.
Pharm. Res. 16(2), 272-280 (1999)

next Lecture

Overview of Dissolution for BA/BE

- **Biopharmaceutics Classification System based on Solubility/Permeability**
  - Various regulatory agencies allow bioequivalence of formulations of BCS Class I drugs to be demonstrated by *in vitro* dissolution ('biowaiver').

United States Food and Drug Administration;
Guidance for Industry: Waiver of In Vivo Bioavailability and Bioequivalence Studies for Immediate-Release Solid Oral Dosage Forms Based on a Biopharmaceutics Classification System. (August 2000)

European Agency for the Evaluation of Medicinal Products / Committee for Proprietary Medicinal Products;
Note for guidance on the investigation of bioavailability and bioequivalence. CPMP/EWP/QWP/1401/98 (July 2001)

next Lecture

Overview of Dissolution for BA/BE

- Biopharmaceutics Classification System based on Solubility/Permeability
- **Biowaivers for BCS I Drugs**
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next Lecture

Overview of Dissolution for BA/BE

- **Biowaivers for BCS I Drugs**
  - Of the 130 orally administered drugs on the WHO list of essential medicines 61 could be classified with certainty, 28 could be provisionally classified, and 41 could not be classified.

    BCS Class I were:
    - 34.4 % (certain, n=61)
    - 39.3 % (provisional, n=28)

next Lecture

Overview of Dissolution for BA/BE

- **Biowaivers for BCS I Drugs**
  - Solubility
    - Based on the highest dosage strength of an IR product
    - Soluble in max. 250 ml of aqueous media
    - pH range 1.0 – 7.5 (FDA), 1.0 – 6.8 (EMEA)
  - Permeability
    - F_a (fraction of dose absorbed) ≥90 %
      - → human *in-vivo* studies
      - → human *in-vitro* studies (CACO-2 cell culture)
    - Absence of evidence suggesting instability in the GI tract

next Lecture

Overview of Dissolution for BA/BE

- **Biowaivers for BCS I Drugs**
  - Dissolution
    - ≥85 % of labeled content dissolved within 30 minutes using

      USP Apparatus I (100 rpm) or

      USP Apparatus II (50 rpm) in a volume of ≤900 ml
      - 0.1 N HCl or Simulated Gastric Fluid USP without enzymes
      - pH 4.5 buffer
      - pH 6.8 buffer or Simulated Intestinal Fluid USP without enzymes
    - ≥12 dosage units
    - Sampling intervals: FDA ≥4, EMEA ≥3

Overview of Dissolution for BA/BE

- **Biowaivers for BCS I Drugs**
  - Excipients
    - Generally, excipients will not affect the rate or extent of absorption of BCS I drugs.
    - Quantity of excipients should be consistent with the intended function (*e.g.*, lubricant).
    - New excipients / atypically large amounts of commonly used excipients: additional information.
      - → Relative BA: aqueous solution as reference
      - → The review division of FDA should by contacted if: large quantities of surfactants (*e.g.*, polysorbate 80) and sweeteners (*e.g.*, mannitol or sorbitol)

next Lecture

Overview of Dissolution for BA/BE

- **Biowaivers for BCS I Drugs**
  - Similarity Factor f_2
    - Not necessary if ≥85 % dissolved in ≤15 minutes in all three dissolution media (FDA).
    - Not more than one mean value of >85% dissolved (EMEA).
    - $f_2 = 50 \cdot \log \{ [1 + (1/n) \Sigma (R_t - T_t)^2]^{-0.5} \cdot 100\}$
    - Coefficient of Variation
      - ➔ ≤20 % at earlier time points (FDA; EMEA no restriction)
      - ➔ ≤10 % at other time points (FDA; EMEA <10 %)
    - Products are considered similar if f_2 ≥50

next Lecture

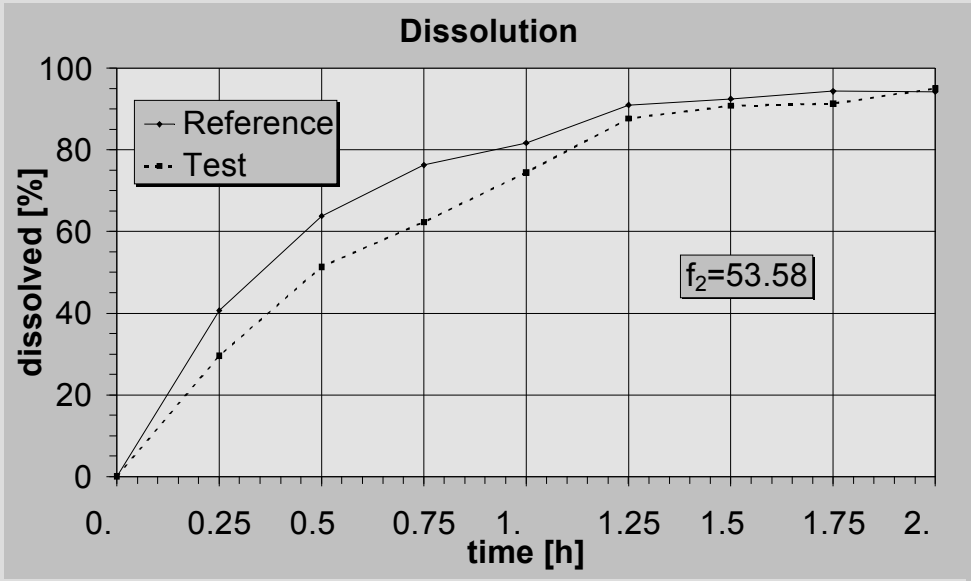
Overview of Dissolution for BA/BE

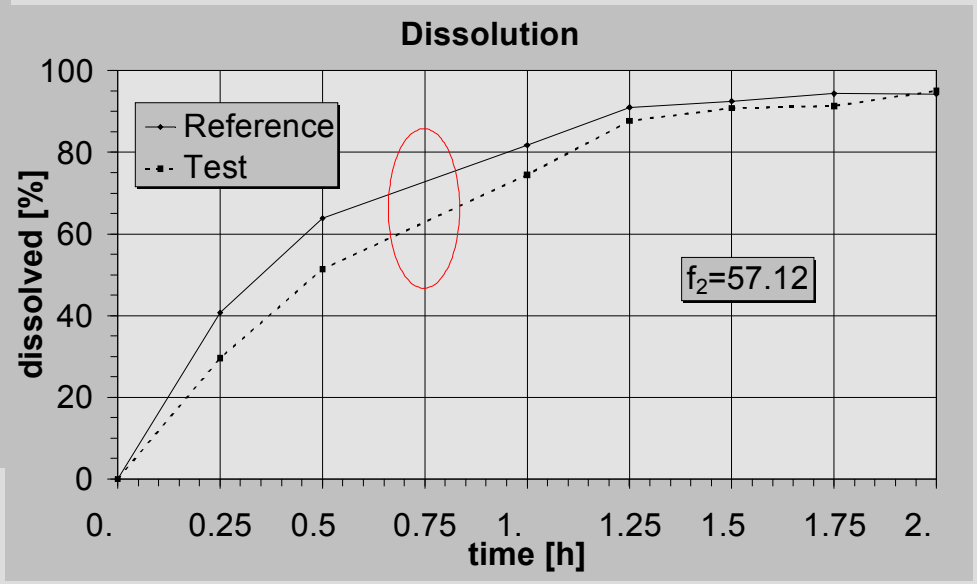
- **Biowaivers for BCS I Drugs**
  - Similarity factor f_2 is an arbitrary measure (not a statistic). Therefore different number of sampling times, and/or different sampling times itself may lead to different conclusions.

Liu, J.-p., Ma, M.-C. and S.-C. Chow;
Statistical Evaluation of Similarity Factor f_2 as a Criterion for Assessment of Similarity Between Dissolution Profiles.
Drug Information Journal 31, 1255-1271 (1997)

Overview of Dissolution for BA/BE

- **Biowaivers for BCS I Drugs**
  - Effect of different number of sampling times

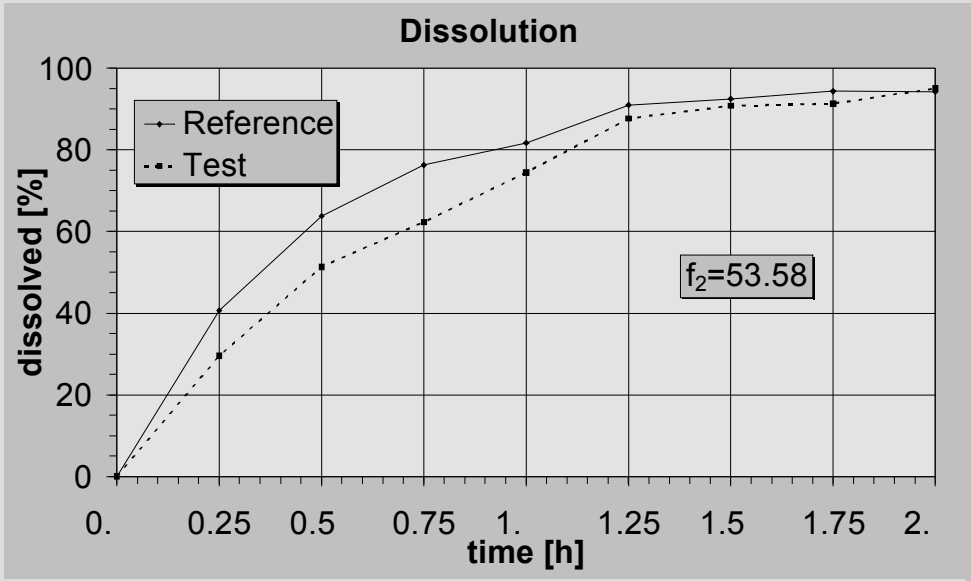


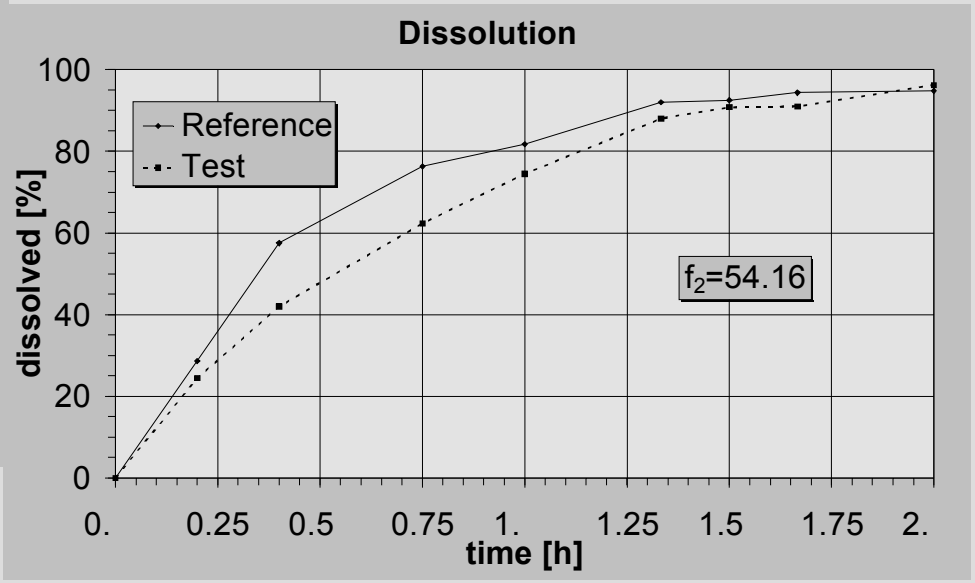


next Lecture

Overview of Dissolution for BA/BE

- **Biowaivers for BCS I Drugs**
  - Effect of different sampling times





Overview of Dissolution for BA/BE

- **Biowaivers for BCS I Drugs**
  - Proposed extensions
    - Current guideline considered conservative (class boundaries of solubility and permeability):
      - permeability: reduce limit of F_a from 0.90 to **0.85**
      - solubility: change pH from 1–7.5 to **1.2–6.8**
      - relax side conditions

Polli, J.E. *et al.*;
Summary workshop report: Biopharmaceutics classification system – implementation challenges and extension opportunities.
J. Pharm. Sci. 93(6), 1375-1381 (2004)

next Lecture

Overview of Dissolution for BA/BE

- Biopharmaceutics Classification System based on Solubility/Permeability
- Biowaivers for BCS I Drugs
- **Discussion of BCS III Drugs**
- Models establishing *in vivo-in vitro* Correlations (IVIVC Levels A-C)

next Lecture

Overview of Dissolution for BA/BE

- **Discussion of BCS III Drugs**
  - Of the 130 orally administered drugs on the WHO list of essential medicines 61 could be classified with certainty, 28 could be provisionally classified, and 41 could not be classified.

    BCS Class III were:
    - 38.2 % (certain, n=61)
    - 37.8 % (provisional, n=28)

Overview of Dissolution for BA/BE

- **Discussion of BCS III Drugs**
  - As proposed by G.L. Amidon biowaivers may also be considered for BCS Class III drugs.
    - High Permeability F_a changed from ≥90 % to 85 % (or 70 %).
    - Allow Waivers at any strength.
    - Reduce number of permeability reference drugs to 10 or 15 (rather than 20).

G.L. Amidon;
BCS: The New Science of Bioequivalence.
BioInternational 2005, London, 24-26 October 2005

next Lecture

Overview of Dissolution for BA/BE

- **Discussion of BCS III Drugs**
  - Example: Acetaminophen (paracetamol)
    - Literature data review: BCS Class III
    - Differences in composition seldom, if ever, have an effect on the extent of absorption.
    - Some studies show differences in rate of absorption between brands and formulations. In particular, sodium bicarbonate, present in some drug products, was reported to give an increase in the rate of absorption, probably caused by an effect on gastric emptying.

next Lecture

Overview of Dissolution for BA/BE

- **Discussion of BCS III Drugs**
  - Example: Acetaminophen (paracetamol)
    - In view of Marketing Authorizations (MAs) given in a number of countries to acetaminophen drug products with rapid onset of action, it is concluded that differences in rate of absorption were considered therapeutically not relevant by the Health Authorities.
    - Moreover, in view of its therapeutic use, its wide therapeutic index and its uncomplicated pharmacokinetic properties, *in vitro* dissolution data collected according to the relevant Guidances can be safely used for declaring bioequivalence (BE) of two acetaminophen formulations.

next Lecture

Overview of Dissolution for BA/BE

- **Discussion of BCS III Drugs**
  - Example: Acetaminophen (paracetamol)
    - Accepting a biowaiver for IR acetaminophen solid oral drug products is considered scientifically justified, if the test product contains only those excipients reported in this paper in their usual amounts and the test product is rapidly dissolving, as well as the test product fulfils the criterion of similarity of dissolution profiles to the reference product.

Kalantzi, L., Reppas, C., Dressman, J.B., Amidon, G.L., Junginger, H.E., Midha, K.K., Shah, V.P., Stavchansky, S.A. and D.M. Barends; Biowaiver monographs for immediate release solid oral dosage forms: Acetaminophen (paracetamol).
J. Pharm. Res. 95(1), 4-14 (2005)

next Lecture

Overview of Dissolution for BA/BE

- Biopharmaceutics Classification System based on Solubility/Permeability
- Biowaivers for BCS I Drugs
- Discussion of BCS III Drugs
- **Models establishing *in vivo-in vitro* Correlations (IVIVC Levels A-C)**

next Lecture

Overview of Dissolution for BA/BE

- **Models etablishing *in vivo-in vitro* Correlations (IVIVC Levels A-C)**
  - **Level A**

    Point-to-point relationship between the *in vitro* dissolution curve and the *in vivo* dissol. curves generated by deconvolution of plasma level data or by other appropriate methods (Wagner-Nelson, Loo-Riegelman, numeric deconvolution).

next Lecture

Overview of Dissolution for BA/BE

- **Models etablishing *in vivo-in vitro* Correlations (IVIVC Levels A-C)**
  - **Level A**
    - One formulation tested at different dissolution conditions compared with a plain aqueous solution of the active substance.
    - Single study with a cross-over design.
    - *In vitro* conditions producing a dissolution profile similar to the *in vivo* input rate.
    - If *in vitro* dissolution is faster/slower than *in vivo* input rate, introduction of a uniform time scaling factor can be considered.

next Lecture

Overview of Dissolution for BA/BE

- **Models etablishing *in vivo-in vitro* Correlations (IVIVC Levels A-C)**
  - **Level B**

    One point relationship between
    - Mean *in vitro* dissolution time of the product / either the mean *in vivo* residence time or the mean *in vivo* dissolution time by using the principles of statistical moment analysis; or
    - *In vitro* dissolution rate constant / the absorption rate constant derived.

next Lecture

Overview of Dissolution for BA/BE

- **Models etablishing *in vivo-in vitro* Correlations (IVIVC Levels A-C)**
  - **Level C**

    One point relationship between amount dissolved *in vitro* at a particular time / one mean PK parameter; if one or several PKPs correlate to the amount of drug dissolved at various time points of the dissolution profile: multi-level C correlation.

next Lecture

Overview of Dissolution for BA/BE

- **Models etablishing *in vivo-in vitro* Correlations (IVIVC Levels A-C)**
  - **Level B/C**

    B/C correlations are not useful for supporting major variations in the composition or manu-facturing process, but can be useful in setting specifications.

next Lecture

Overview of Dissolution for BA/BE

- **Models etablishing *in vivo-in vitro* Correlations (IVIVC Levels A-C)**
  - Predictability…
    - The less data available for development and evaluation of the IVIVC, the more additional data needed for the complete evaluation of the predictability of the IVIVC.
    - Formulations studied should differ adequately in release rate (*e.g.*, ≥10 % dissolved) resulting in substantial difference in the pharmacokinetic parameters of interest.

European Agency for the Evaluation of Medicinal Products / Committee for Proprietary Medicinal Products;
Note for Guidance on Quality of Modified Release Products: A: Oral Dosage Forms. B: Transdermal Dosage Forms. Section I - Quality. (July 1999)