Topic – Bioavailability and Bioequivalence

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BIOAVAILABILITY & BIOEQUIVALENCE

- "The term Bioavailability is defined as a rate & extent (amount) of absorption of unchanged drug from its dosage form."

  - Brahmankar & Jaiswal


THE FAMILY CIRCUS.
By Bil Keane
2-3
Copyright 1978
The Register and Tribune
Syndicate, Inc.
"How will that stuff get from down there up to my sore throat?"

Objectives of Bioavailability studies :

- During primary stages of development of suitable dosage forms of new drug entity .
- Determination of influence of excipients , patient related factors & possible interaction with other drugs on the efficiency of absorption .
- Development of new formulations of existing drugs .

Significance of Bioavailability

- Drugs having low therapeutic index, e.g. cardiac glycosides, quinidine, phenytoin etc
- Narrow margin of safety (e.g. antiarrythmics, antidiabetics, adrenal steroids, theophylline)
- Drugs whose peak levels are required for the effect e.g. phenytoin, phenobarbitone, primidone, sodium valporate, anti-hypertensives,antidiabetics and antibiotics.
- Drugs that are absorbed by an active transport,e.g. amino acid analogues. Purine analogues etc.

- Drugs which are disintegrated in the alimentary canal and liver, e.g.chiorpromazine etc. or those which under go first pass metabolism.
- Formulations that give sustained release of drug.
- Any new formulation has to be tested for its bioavailability profile.
- Drugs with steep dose response relationship i.e. drugs obeying zero order kinetics / mixed order elimination kinetics (e.g. warfarin , phenytoin, digoxin, aspirin at high doses, phenylbutazone)

"I stopped taking the medicine because I prefer the original disease to the side effects."

Bioavailable fraction (F)

- It refers to the fraction of administered dose that enters the systemic circulation.

$$F = \frac{\text{Bioavailable dose}}{\text{Administered dose}}$$

Absolute Bioavailability (F)

- Def :

  "When the systemic availability of a drug administered orally is determined in comparison to its intravenous administration ,is called as Absolute Bioavailability"

$$\% \text{ Absorption} = \frac{\text{Dose (iv)} \times \text{AUC (oral)}}{\text{Dose (oral)} \times \text{AUC (iv)}} \times 100$$

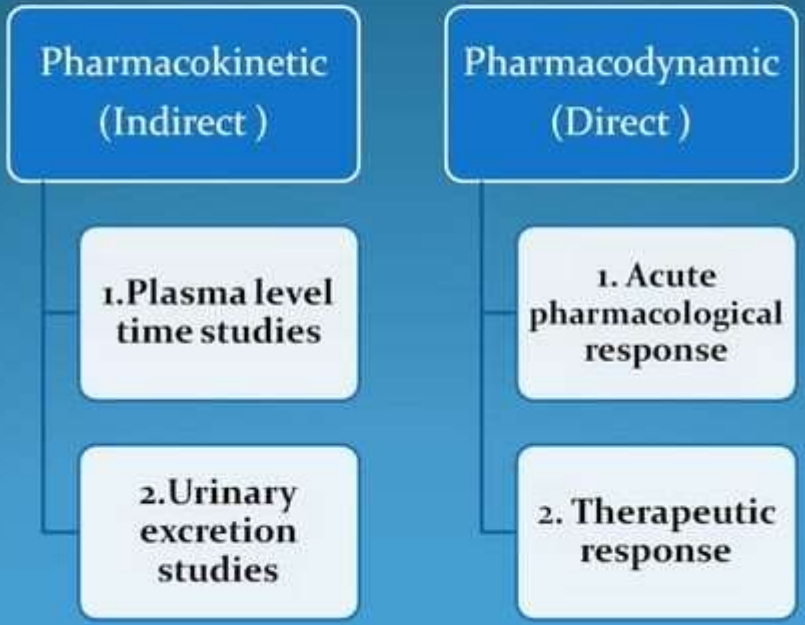
Relative Bioavailability (Fr)

- Def :

  " When the systemic availability of the drug after oral administration is compared with that of oral standard of same drug (such as aqueous or non aqueous solution or a suspension) is referred as Relative Bioavailability"

  e.g. comparison between ***cap.*** Amox and ***susp.*** Amox

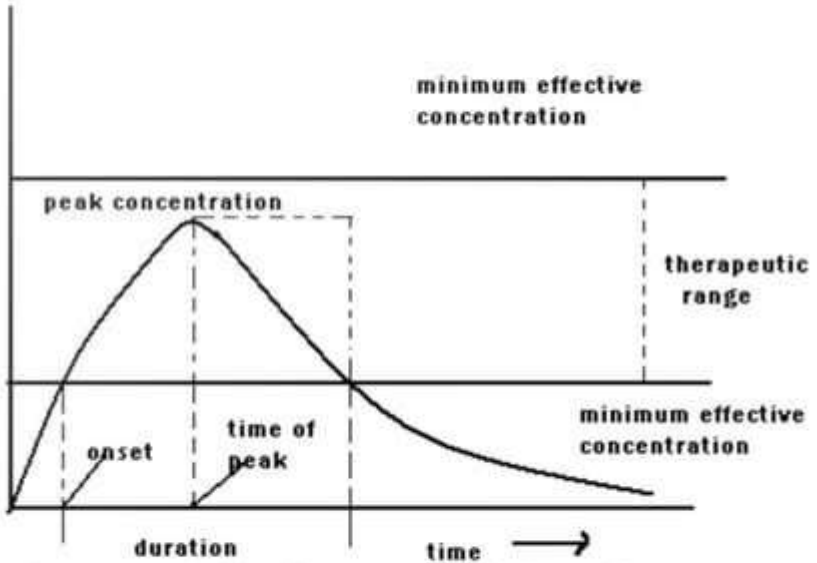
Measurement of Bioavailability



1) Plasma level-time studies:

- Two dosage forms that exhibit super imposable plasma level-time profiles should result in identical therapeutic response.

$$F = \frac{[AUC]_{oral} \times [D]_{iv}}{[AUC]_{iv} \times [D]_{oral}}$$



plasma concentration-time curve foll single oral dose
a-b absorption phase of curve
c-d elimination phase of curve

Based on the plasma concentration-time curve, the following measurements are important for bioavailability studies.

- MINIMUM EFFECTIVE PLASMA CONCENTRATION-The minimum plasma concentration of the drug required to achieve a given pharmacological or therapeutic response. This value varies from drug to drug and from individual to individual as well as with the type and severity of the disease.

- MAXIMUM SAFE CONCENTRATION-The plasma concentration of the drug beyond which adverse effects are likely to happen.

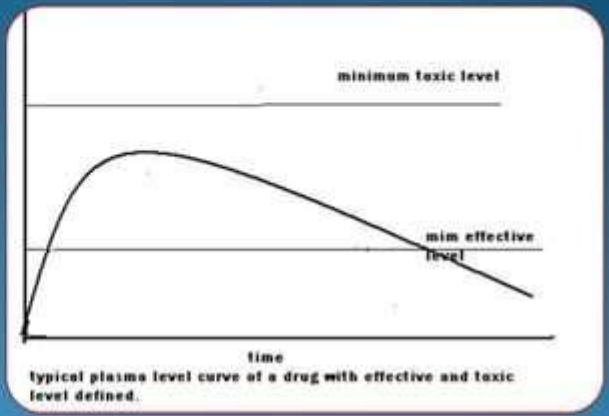
THERAPEUTIC RANGE-The range of plasma drug concentration in which the desired response is achieved yet avoiding adverse effect. The aim is clinical practice is to maintain plasma drug concentration within the therapeutic range.

ONSET OF ACTION-On set of action is the time required to achieve the minimum effective plasma concentration following administration of drug formulation.

DURATION OF ACTION-Duration of action of the therapeutic effect of the drug is defined as the time period during which the plasma concentration of the drug exceeds the minimum effective level.

INTENSITY OF ACTION-In general, the difference between the peak plasma concentration and the minimum effective plasma concentration provides a relative measure of the intensity of the therapeutic response of the drug.

- Important parameters
  - C_{max} - peak plasma concentration

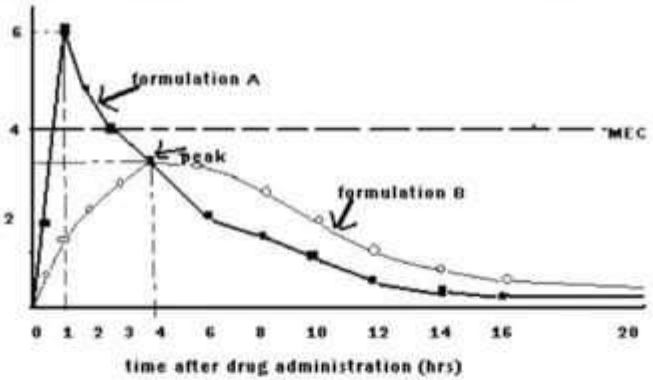


typical plasma level curve of a drug with effective and toxic level defined.

  - t_{max} - time taken to reach peak concentration
    - it indicates rate of absorption
  - AUC - Area Under the plasma level time Curve

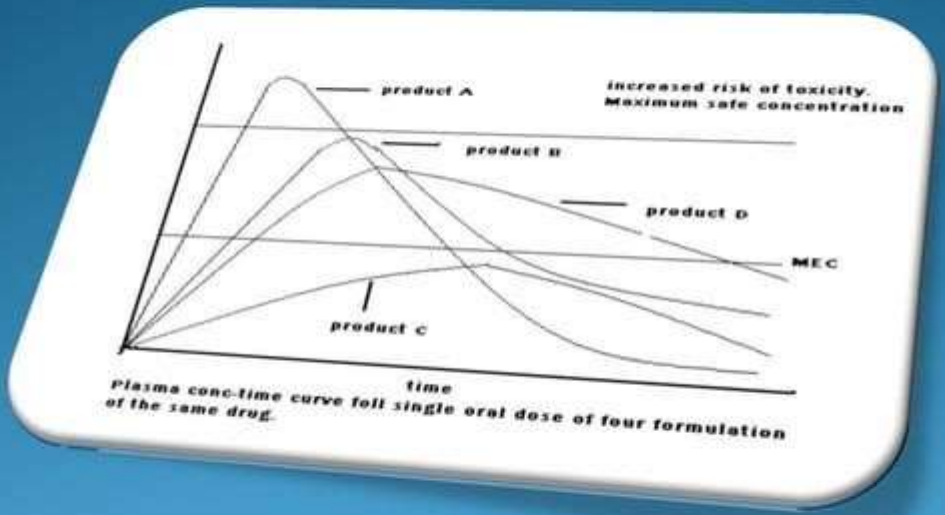
    give the measure of extent of absorption

On the other hand, if the two curves represent blood concentrations following equal doses of two different formulations of the same cardiac glycoside



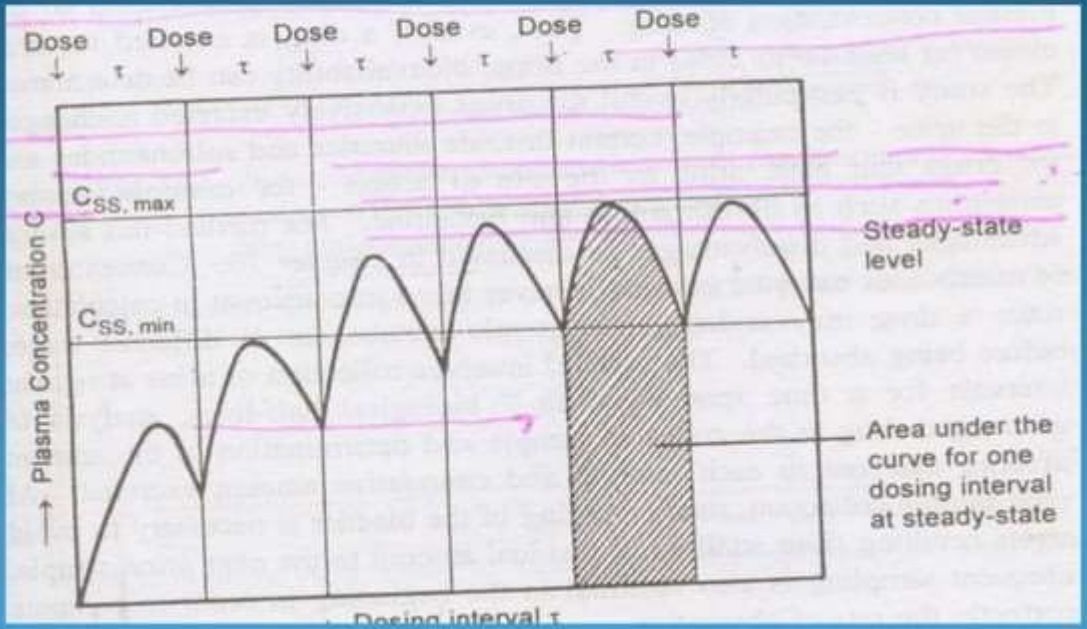
blood conc-time curves obtained for two different formulations of the same drug demonstrating relationship of the profiles to the minimum effective concentration

An example can explain how difference in bioavailability of a given drug from different formulations marketed by various firm, can result in a patient being either over, under or correctly medicated.



Product D is more desirable form of a dosage form specially for drugs with narrow safety margin and relatively shorter half life.

In multiple dose study:



b) URINARY EXCRETION-

This method can be based if urinary excretion of unchanged drug is the main mechanism of elimination of the drug

- *Bioavailability can be calculated as follows,*

$$F = \frac{(Du\infty)}{f}$$

F = Fraction of the dose absorbed
Du∞ = cumulative amount of drug excreted in the urine
f = fraction of unchanged drug excreted in the urine

5x the elimination ½ life = time at which the drug is "completely" (97%) eliminated from the body

1x ½ life - 50% of the original drug removed
2x ½ life - 75%
3x ½ life - 87.5%
4x ½ life - 93.75%
5x ½ life - 96.875%

- **Urinary excretion ∝ plasma concentration of drug**
- Mainly used in drugs extensively excreted unchanged in urine.
  - E.g. Thiazide diuretics
    Sulfonamides
    Urinary antiseptics : nitrofurantoin , Hexamine.

$$F = \frac{[Xu\infty]oral \times D\,iv}{[Xu\infty]iv \times D\,oral}$$

a. $(dX_u / dt)_{max}$: Maximum urinary excretion rate

b. $(t_u)_{max}$: Time for maximum urinary excretion rate

c. X_u : Cumulative amount of drug excreted in the urine.

Biological fluids used for determination of Bioavailability

1. Plasma
2. Urine
3. Saliva
4. CSF
5. Bile

B. Pharmacodynamic methods

1) Acute Pharmacological Response :

- Used when pharmacokinetic methods are difficult , inaccurate & non reproducible.

- E.g. Change in ECG/EEG readings.
  Pupil diameter

Disadvantages :

- More variable
- Active metabolite interferes with the result.

2) Therapeutic Response :

- measurement of clinical response to a drug formulation given to patients suffering from disease for which it is intended to be used.

Disadvantages :

Improper quantification of observed response.

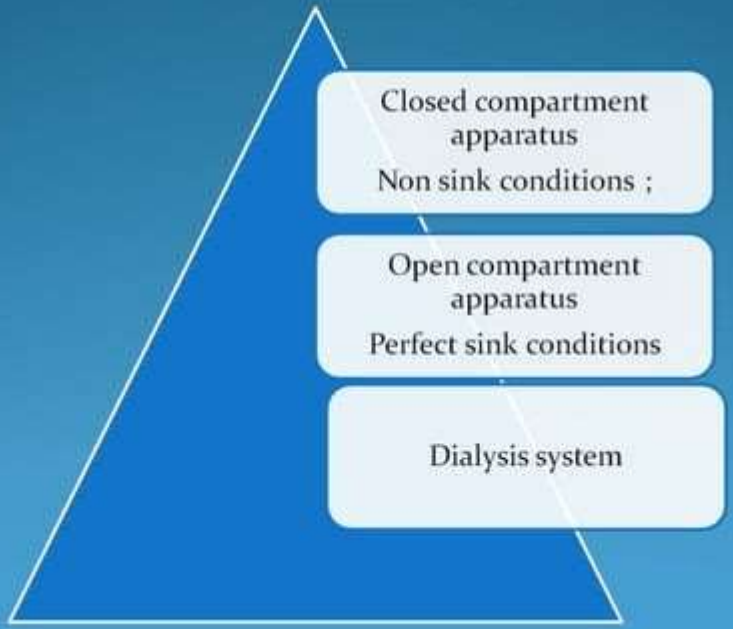
Drug dissolution rate & Bioavailability :

- Correlation between Dissolution testing and bioavailability

- **In vivo determination test :**
  - Tool in the development of new dosage form.

- **In vitro dissolution test** :
  - To ensure batch to batch consistency
  - Best available tool which can quantitatively assure about bioavailability.

Drug Dissolution Apparatus



In vitro drug dissolution rate and bioavailability

Factors to be considered:

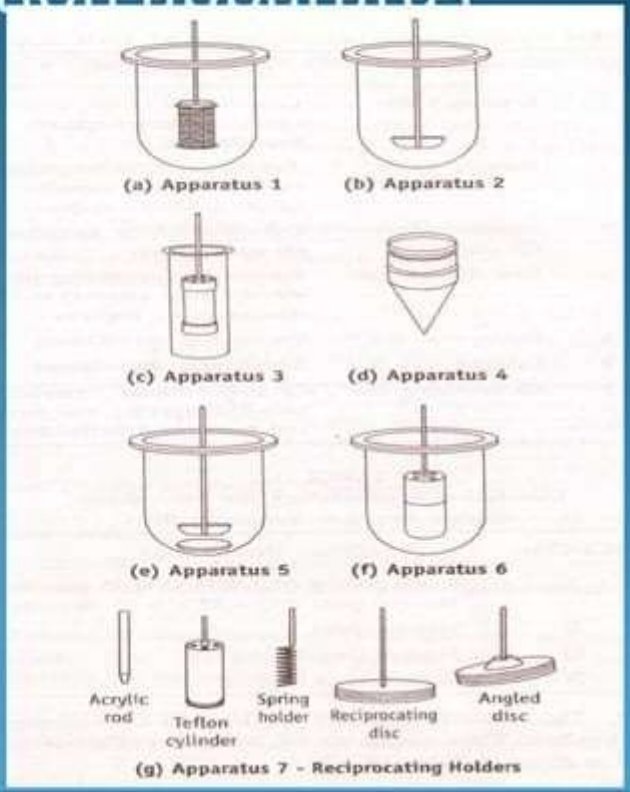
1. Factors relating to dissolution apparatus
2. Factors relating to dissolution fluid
3. Process parameters

Types of dissolution apparatus

- Closed compartment
- Open compartment

- Official compendial methods:

1. Rotating basket
2. Rotating paddle
3. Reciprocating cylinder
4. Flow-through cell
5. Paddle over disc
6. Cylinder apparatus
7. Reciprocating disc



Compendial Dissolution Apparatus Types and Their Applications

Apparatus	*Name*	*Drug Formulation Tested*
Apparatus 1	Rotating basket	Conventional tablets, chewable tablets, controlled-release formulations
Apparatus 2	Rotating paddle	Tablets, orally disintegrating tablets, chewable tablets, capsules, controlled-release products, suspensions
Apparatus 3	Reciprocating cylinder	Controlled-release formulations, chewable tablets
Apparatus 4	Flow-through cell	Formulations containing poorly soluble drugs, powders and granules, microparticles, implants
Apparatus 5	Paddle over disc	Transdermal formulations
Apparatus 6	Cylinder	Transdermal formulations
Apparatus 7	Reciprocating disc	Controlled-release formulations (non-disintegrating oral formulations and transdermal formulations)

Dissolution acceptance criteria

- Q is defined as percentage of drug content dissolved in a given time period.

Dissolution Acceptance Criteria

Stage	*Number of Dosage Units Tested*	*Acceptance Criteria*
S_1	6	No dosage unit is less than Q+5%
S_2	6	Average of the twelve dosage units ($S_1 + S_2$) $\geq$ Q% and no dosage unit is less than Q-15%
S_3	12	Average of the twenty four dosage units ($S_1 + S_2 + S_3$) $\geq$ Q% and not more than two dosage units are less than Q-15% and no dosage unit is less than Q-25%

Objectives of dissolution profile comparison

- Development of bioequivalent drug products.
- Demonstrating equivalence after change in formulation of drug product.
- Biowaiver of drug product of lower dose strength in proportion to higher dose strength product containing same active ingredient and excipients.

Method for comparison of dissolution profile

- Based on the determination of difference factor f_1 and similarity factor f_2

$$f_1 = \frac{\sum_{t=1}^{n} (R_t - T_t)}{\sum_{t=1}^{n} R_t} 100$$

$$f_2 = 50 \log \left\{ \left[1 + \frac{1}{n} \sum_{t=1}^{n} (R_t - T_t)^2 \right]^{-0.5} 100 \right\}$$

where n = number of dissolution time points
R_t = dissolution value of the reference drug product at
T_t = dissolution value of the test drug product at time t

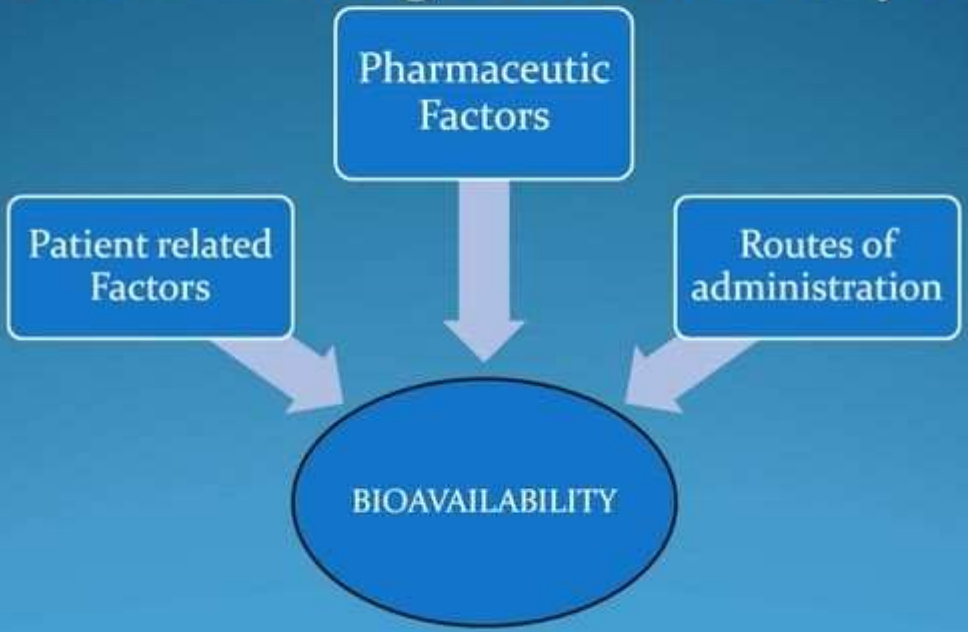
Comparison of Dissolution Profile

Difference factor f_1	*Similarity factor f_2*	*Inference*
0	100	Dissolution profiles are identical
≤ 15	≥ 50	Similarity or equivalence of two profiles

The evaluation of similarity between dissolution profiles is based on following ***conditions*** –

- Minimum of three dissolution time points are measured.
- Number of drug products tested for dissolution is 12 for both test and reference.
- Not more than one mean value of > 85% dissolved for each product.
- Standard deviation of mean of any product should not be more than 10% from second to last dissolution time point.

Factors affecting Bioavailability :



A) Pharmaceutic factors :

1) Physicochemical properties of drug :

1. Drug solubility & dissolution rate.
2. Particle size & effective surface area.
3. Polymorphism & Amorphism.
   - Amorphous > metastable > stable
4. Pseudopolymorphism (Hydrates / Solvates)
   - Anhydrates > hydrates e.g. Theophylline, Ampicillin
   - Organic solvates > non solvates e.g. fludrocortisone
5. Salt form of the drug.
   - Weakly acidic drugs – strong basic salt e.g.barbiturates , sulfonamides.
   - Weakly basic drugs – strong acid salt
6. Lipophilicity of the drug .
7. pKa of the drug & pH .
8. Drug stability.

2) Dosage form characteristics & Pharmaceutic Ingredients :

1. Disintegration time (tab/cap)
2. Dissolution time.
3. Manufacturing variables.
4. Pharmaceutic ingredients (excipients / adjuvants)
5. Nature & type of dosage form.
   - Solutions> Emulsions> Suspensions> Cap> Tab> Enteric Coated Tab > Sustained Release
6. Product age & storage conditions.

B) Patient related factors :

1. Age
2. Gastric emptying time .
3. Intestinal transit time .
4. Gastrointestinal pH .(HCL > Acetic > citric)
5. Disease States .
6. Blood flow through the gastrointestinal tract .
7. Gastrointestinal contents :
    a) Other drugs .
    b) Food .
    c) Fluids
    d) Other normal g.i. contents
8. Presystemic metabolism (First – Pass effect) by :
    a) Luminal enzymes .
    b) Gut wall enzymes .
    c) Bacterial enzymes .
    d) Hepatic enzymes .

In Vitro-in vivo correlation

- A predictive mathematical model that describes the relationship between an in-vitro property of a dosage form and an in-vivo response.

Purpose of IVIVC

- The optimization of formulations may require changes in the composition, manufacturing process, equipment, and batch sizes.
- In order to prove the validity of a new formulation, which is bioequivalent with a target formulation, a considerable amount of efforts is required to study bioequivalence (BE)/ bioavailability (BA).
- The main purpose of an IVIVC model - to utilize *in vitro* dissolution profiles as a surrogate for *in vivo* bioequivalence and to support biowaivers.

Basic approaches

- By establishing a relationship usually linear, between the in vitro dissolution and in vivo bioavailability parameters.
- By using data from previous bioavailability studies to modify the dissolution methodology.

In vitro-in vivo correlations

- Correlations based on the plasma level data
- Correlations based on the urinary excretion data
- Correlations based on the pharmacological response

IVIVC levels

- Level A:
  - Point to point correlation is developed between in vitro dissolution rate and the in vivo rate of absorption
- Level B:
  - Utilises statistical moment analysis and the mean in vitro dissolution time is compared to either the mean residence time or the mean in vivo dissolution time
- Level C:
  - single point correlation that relates one dissolution time point to one pharmacokinetic parameter

Multiple level C

S.No	*In Vitro*	*In Vivo*
	% Dissolution profile	**Plasma concentration Time profile**
1	% drug dissolved at time t	Plasma con at time t
2	Max drug dissolved at t	C_{max}
3	Time taken for max extent of drug release	T_{max}
4	Total amount of drug dissolution	AUC_0, AUC_∞
5	Time for a certain % of drug to dissolve	Time for a certain % drug reaches the circulation
	Kinetic Parameter	**Pharmacokinetic parameter**
6	Dissolution rate constant	Absorption rate constant
7	Dissolution half life	Absorption half life
8	% of drug dissolved at time t	% drug absorbed at time t
	Statistical moment analysis	
9	MDT (mean Dissolution Time)	MRT (mean residence time)

BCS Classifications

According to the BCS, drug substances are classified as follows:

- *Class I - High Permeability, High Solubility*
- *Class II - High Permeability, Low Solubility*
- *Class III - Low Permeability, High Solubility*
- *Class IV - Low Permeability, Low Solubility*

Biopharmaceutics Drug Classification System for Immediate-Release Drug Products and IVIVC Expectations

Class	*Solubility*	*Permeability*	*IVIVC expectations for immediate-release product*	*Possibility of predicting IVIVC from dissolution data*
I	High	High	IVIVC expected, if dissolution rate is slower than gastric emptying rate, otherwise limited or no correlation.	Yes
II	Low	High	IVIVC expected, if *in vitro* dissolution rate is similar to *in vivo* dissolution rate, unless dose is very high.	Yes
III	High	Low	Absorption (permeability) is rate determining and limited or no IVIVC with dissolution.	No
IV	Low	Low	Limited or no IVIVC is expected.	No

Biopharmaceutics Drug Classification System for Extended-Release Drug Products and IVIVC Expectations

Class	*Solubility*	*Permeability*	*IVIVC*
Ia	High and site independent	High and site independent	IVIVC Level A expected
Ib	High and site independent	Dependent on site and narrow absorption window	IVIVC Level C expected
IIa	Low and site independent	High and site independent	IVIVC Level A expected
IIb	Low and site independent	Dependent on site and narrow absorption window	Little or no IVIVC
Va: Acidic	Variable	Variable	Little or no IVIVC
Vb: Basic	Variable	Variable	IVIVC Level A expected

BIOEQUIVALENCE

- Definition :

  " It is a relative term which denotes that the drug substance in two or more identical dosage forms , reaches the circulation at the same relative rate & to same relative extent i.e. their plasma concentration-time profiles will be identical without significant statistical differences."

- **Pharmaceutical equivalence** :

  "Drug products are considered to be pharmaceutical equivalents if they contain the same active ingredients and are identical in strength or concentration, dosage form, and route of administration."

- **Therapeutic equivalence** :

  " It indicates that two or more drug products that contain the same therapeutically active ingredient, elicit identical pharmacological effects & can control the disease to the same extent"

- **Clinical equivalence**:

  " when the same drug from two or more dosage forms gives identical in vivo effects as measured by a pharmacological response or by control of a symptom or a disease."

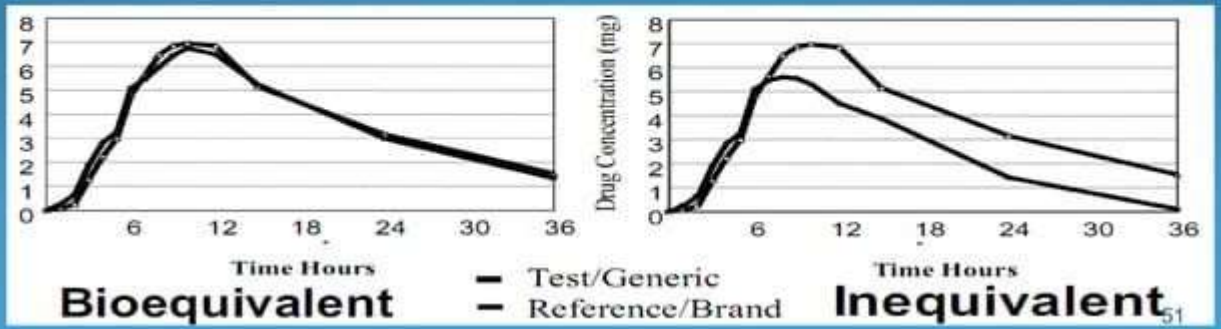
When do we do BE studies ?

- ✓ Clinical Service Form to Final Market Form
- ✓ Change of formulations (capsules to tablet)
- ✓ Generic Formulations
- ✓ Change of Process or manufacturing site (some times)
- ✓ Regulatory requirement.
- ✓ Establishment of pharmacokinetic parameters.
- ✓ Study of formulations & process variables.

What is Bioequivalence?

A generic drug is considered to be bioequivalent to the brand name drug if:

- The rate and extent of absorption do *not show a significant difference from listed drug, or*
- The extent of absorption does *not show a significant difference and any difference in rate is intentional or not medically significant*



Two kinds of drugs

- A brand name drug
  - An Innovator drug.
  - Price of new medicine
- A generic drug
  - Drug which contains the same active ingredient in the same formulation as the brand name.
  - A generic drug cannot be marketed in the US until the patent on the innovator drug has expired.
  - Same efficacy, but usually cheaper.

THE CRITICAL PATH TO MEDICAL DRUG DEVELOPMENT

New Chemical Entities (NCEs)

Conceptual chemistry

Lead optimization

Preclinical biology

ADME

Toxicology

Regulatory approval for Human studies

Phase I – III Clinical trials

Regulatory Dossier

[Time frame : 8 -10 years; Cost : ~$1 bio]

Generics

API Process Research (GMP)

Formulation Development (GMP)

Bioequivalence study (GCP)

Regulatory Dossier

[Time frame : 2-3 years;
Cost : $6-10 mio]

Brand Drugs vs Generic Drugs

Brand Name Drug

Patent

- Generally 10 years

Name

- Marketing Purpose
- Tylenol
- Advil
- Mylanta

Price

- Expensive

Generic Drug

Patent

- After Patent

Name

- Chemical Element
- Acetaminophen
- Ibuprofen
- Antacids

Price

- 30-84% Cheap

NDA vs. ANDA Review Process

Original Drug

NDA Requirements

1. Chemistry
2. Manufacturing
3. Controls
4. Labeling
5. Testing
6. Animal Studies
7. Clinical Studies

(Bioavailability/Bioequivalenc
e)

Generic Drug

ANDA Requirements

1. Chemistry
2. Manufacturing
3. Controls
4. Labeling
5. Testing
6. Bioequivalence Study (In Vivo, In vitro)

Note: Generic drug applications are termed **"abbreviated"** because they are generally **not required to include preclinical (animal)** and **clinical (human) data to establish safety and effectiveness**.
Instead, generic applicants must scientifically demonstrate that their product is bioequivalent (i.e., performs in the same manner as the origina; drug).

- However bioequivalence is not straight forward for all the drugs . Many drugs shows bioinequivalence.
- In 1973 ad hoc committee on drug product selection of American Pharmaceutical Association published a list of drug that show bioinequivalence.
- Based on this list drug has been divided into 3 categories

HIGH RISK POTENTIAL	MODERATE RISK POTENTIAL	LOW RISK POTENTIAL
Aminophylline	Amphetamine	Acetaminophen
Bishydroxy coumarine	Ampicillin	Codeine
Digoxin	Chloramphenicol	Hydrochlorothiazide
phenytoin	Digitoxin	Ephedrine
prednisolone	Erythromycin	Isoniazide
prednisone	Griesofulvin	Meprobamate
quinidine	Penicillin G	Penicillin V
warfarin	Pentobarbital	Sulfixazole

BIOEQUIVALENCE PROBLEMS

Bioequivalence problem occurs due to following reason-

- Active drug ingredient has low solubility in water . (less than 5 mg/ml) .
- Dissolution rate is low.
- Certain structural forms of active drug ingredient (e.g. polymorphic forms, solvates, complexes & crystal modifications) dissolve poorly, thus altering the absorption.
- Drug product that have high ratio of excipients to active ingredients (e.g. greater than 5:1) .
- Specific ingredients such as hydrophilic & hydrophobic excipient & lubricant may interfere with absorption .
- Active ingredients absorbed in particular segment of GIT.
- Rapid metabolism in intestinal wall or in liver during absorption process.

Limitations of BA/BE studies

- Difficult for drugs with a long elimination half life.
- Highly variable drugs may require a far greater number of subjects
- Drugs that are administered by routes other than the oral route
- Drugs/dosage forms that are intended for local effects have minimal systemic bioavailability.

  E.g. ophthalmic, dermal, intranasal and inhalation drug products.
- Biotransformation of drugs make it difficult to

  evaluate the bioequivalence of such drugs :e.g. stereoisomerism

Study Protocol

1.Title

a) Principle investigator(Study director)

b) Project/protocol number & date.

2.Study objective

3. Study design

a) Design

b) Drug products

1.Test products

2. Reference Product

c) Dosage regimen

d) Sample collection schedule

e) Housing/ confinement

f) Fasting/meal schedule

g) Analytical methods

4. Study population

a) Subjects

b) Subject selection

1. Medical history
2. Physical examination.
3. Laboratory test.

c) Inclusion and exclusion criteria

d) Restriction / prohibitions

5. Clinical procedures

A) Dosage and drug administration

B) Biological sampling schedule

C) Activity of subject

6. Ethical Consideration

A) Basic principles

B) Institutional review board

C) Informed consent

D) Adverse reactions

7. Facilities

8. Data analysis

A) Analytical validation procedure

B) Statistical treatment of data

9. Drug accountability

10. Appendix

INFRASTRUCTURE

- Clinical
  - A clinical pharmacology unit with atleast a 30-bed ward.
  - Healthy volunteer pool
  - Access to an accredited path lab
  - Pharmacy with controlled access
  - Phlebotomy area and biological waste disposal
  - Sample store with freezers
  - Access to an ICU
  - Dining area, recreation area and toilets
  - Kitchen/pantry with standardised menus
- Bioanalytical
  - A bioanalytical laboratory with modern analytical equipment (HPLC and LC/MS)
  - Sample processing lab with fume hoods
  - Sample store
  - PK and statistical support

1. Title
   a. Principle Investigator
   b. Project number & Date

2. Study Objective

3. Study Design

a. Design
b. Drug Products
   Test
   Reference
c. Dosage Regimen
d. Sample collection schedule
e. Housing
f. Fasting/ meals schedule
g. Analytical methods

BE STUDY : TYPICAL SINGLE DOSE DESIGN

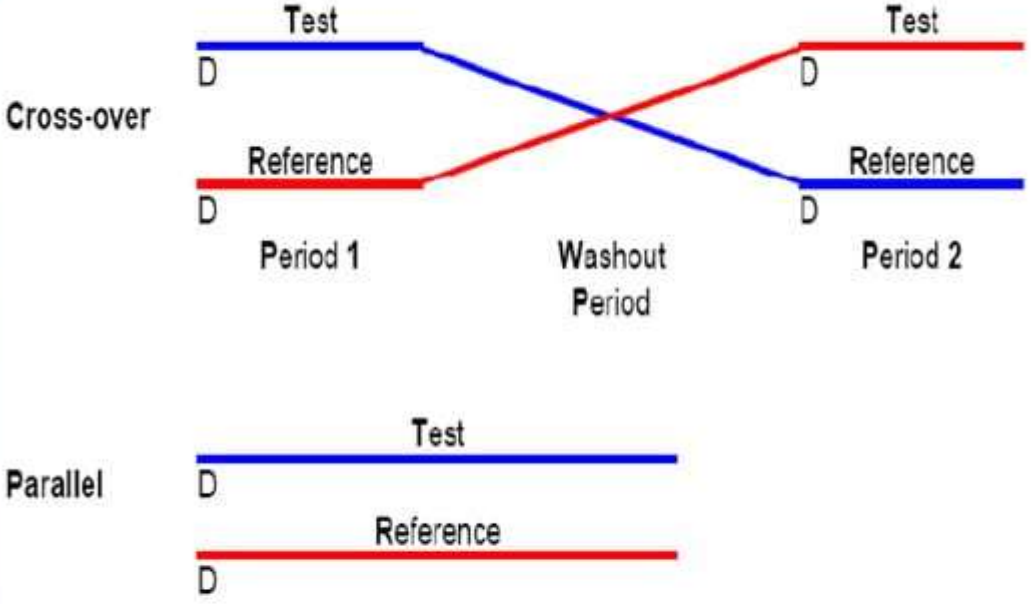
- 2-drug products, 2-period, 2-sequence, cross-over design.
- 2-drug products : the innovator drug (Reference) and the generic drug product (Test).
- 2-period : Single doses of the drug are administered on two occasions (Period I and Period II) with adequate wash-out duration in between (generally 8 to 10 half-lives of the drug).
- Sampling time : 12-20 blood samples to cover 3 or more terminal half-lives (maximally until 72 hours).
- PK Data analysis : Peak exposure (Cmax) and total systemic exposure, i.e., Area under curve (AUC).

Group	Period I (dayı)	Period II (8 day)
I	T	R
II	R	T

- Thus sequence of administration for group I is T-R & group II is R-T .
- Two formulation trial is always a 2 period trial,
- Thus in period I , 50% subject (group I) receive T & 50% subject (group II) receive R .
- In period II order is reversed

WASHOUT PERIOD

- Time interval between two treatments.
- At least **10** half lives between **2** treatments.
- Ensure **99.9%** elimination, Max carry over: **0.1%.**
- It is a function of $t_{1/2}$ and dose of drug administered.
- Metabolites should be eliminated.
- Wash out period: 1 week.


Cross-over
Test
D
Reference
D
Test
D
Reference
D
Period 1
Washout Period
Period 2
Parallel
Test
D
Reference
D

1. Parallel Design

Formulations administered randomly to two groups of volunteers.

Disadvantage

Inter subject variability › formulation variability.

2.Cross over design

- Minimizes inter subject variability.
- Uses each subject as his or her own control

a) Latin Square Cross Over Design

1. Randomised,balanced, complete cross over design.
2. Each subject receives just once each formulation.
3. Each formulation is administered only once in each study period.

LATIN –SQUARE CROSS OVER DESIGN FOR BIOEQUIVALENCE STUDY OF 3 DRUG PRODUCTS IN 6/12 HUMAN VOLUNTEERS

SUBJECT	STUDY PERIOD 1	STUDY PERIOD 2	STUDY PERIOD 3
1, 7	A	B	C
2, 8	B	C	A
3, 9	C	A	B
4, 10	A	C	B
5,11	C	B	A
6, 12	B	A	C

2 way & 3 way cross over design

Two Way Crossover

Group No.	Subjects in Groups	Treatment for Period No.	
		1	2
1	1,2,3,4,5,6	A	B
2	7,8,9,10,11,12	B	A

Three Way Crossover

Group No.	Subjects in Group	Treatment for Period No.		
		1	2	3
1	1,2,3,4,5,6	A	C	B
2	7,8,9,10,11,12	B	A	C
3	13,14,15,16,17,18	C	B	A

Advantages of cross over design

- Minimizes the effect of inter subject variability.
- Minimizes the time effect on bioavailability since each dosage form is administered in each study period.
- Requires less number of subjects to get meaningful results.

Disadvantages of cross over design

- Requires longer time to complete the study.
- Longer is the $t_{1/2}$ greater is time required.
- Greater the no. of formulations to be evaluated more the time for trials.
- Subjects drop out due to increased study periods.

b) Balanced Incomplete Block Design (BIBD)

- ✓Four formulations :A,B,C,D
- ✓Each subject receives n.m.t 2 formulations
- ✓Each formulation is administered same no. of times
- ✓Each pair of formulations occurs together in the same number of subjects
- ✓Each formulation administered: 6 times
- ✓Each subject receives: 2 formulations

Subject	I	II
1	A	B
2	B	A
3	A	C
4	C	A
5	A	D
6	D	A
7	B	C
8	C	B
9	B	D
10	D	B
11	C	D
12	D	C

Reference & Test Product

- Before proceeding study both the test product & reference product are tested for in vitro dissolution profile.

- Dosage regimen - the manner in which drug is taken
- An optimal multiple dosage regimen is - In which the drug is administered in suitable doses, with sufficient frequency that ensures maintenance of plasma concentration with in the therapeutic window for the entire duration of study.

Single Vs Multiple Dose Studies

- **Single**
  - Bioequivalence study.
  - Dosage forms meant for single dose administration.
  - Very Common.
  - Easy, offer less exposure to drugs, less tedious.
  - Difficult to predict steady state characteristics of drug and

Multiple

1.Specialized dosage forms.
(Time release, enteric coated, I.M depot preparations)

2. Drugs undergoing first pass metabolism.

3. Specialized Dosage regimen.

- **Disadvantages**

a) Difficult to control.

b) Exposes the subject to more drug, highly tedious, time consuming.

Sampling

- Sampling should be frequent enough to define the absorption phase, C_{max}, elimination phase during a drug's time course.
- Enough data points should be available to determine K_a and AUC.
- Sampling to be carried out till the linear elimination phase.
- For 1st order process time required for complete elimination is ∞.

Study Conditions

- Subjects maintained on uniform diet.
- No drug one week prior to the study.
- Condition to define-

1. fasting period before administration.
2. fluid intake & volume to be allowed.
3. fasting after administration.

4. Study Population

a. Subjects
b. Subject selection
    Medical history
    Physical examination
    Laboratory Tests
a. Inclusion/ exclusion criteria
b. Restrictions/ Prohibitions

BE STUDY POPULATION

- Should be ≥ 18 years of age and capable of giving informed consent, representing the general population (age, gender and race).
- If the drug product is intended for both genders, the sponsor should attempt to include equal number of males and females.
- If the drug product is to be used predominantly in the elderly, the sponsor should attempt to include subjects of 60 years or older in the study with a target of 40% elderly subjects analysed.
- No subgroup analysis is needed for statistical procedures.

Selection of Subjects

- **Patients as Volunteers**
- **Advantages**

1. Mimics actual conditions of usage.
2. Patient may be benefitted from the study.
3. Reflects better therapeutic efficiency of drug.
4. Avoids ethical issues of administering drugs to healthy subjects.
5. Drug absorption patterns in disease states can be evaluated.
6. Preferred for Multidose availability studies.

- Healthy human volunteers :
  i. Young
  ii. Healthy
  iii. Male
  iv. Body wt. within narrow range.
  v. Restricted dietary & fixed activity conditions.

5. Clinical Procedures

a. Dosage & Drug Administration
b. Biological sampling schedule
c. Activity of subjects

6. Ethical considerations

a. Basic Principles
b. Institutional review board
c. Informed consent
d. Indications for subject withdrawal
e. Adverse reactions & Emergency procedures

7. Facilities

8. Data Analysis

a. Analytical validation Procedure
b. Statistical treatment of data

Bioanalytical Method Validation

Method Validation should include

Accuracy

Precision

Sensitivity

Specificity

Recovery

Stability

STATISTICAL ANALYSIS OF DATA

Purpose:

- Test formulation gives a blood level profile identical to the reference standard.
- Biological and experimental variation does exist due to limitations in the sampling technique.
- Necessary to ascertain whether these differences are simply chance occurrence or are due to actual differences in the treatment administered to the patient.
- Sources of variation:
    1. Subjects
    2. Period
    3. Formulation
    4. Order

- **Statistical methods are used to evaluate the data in order to identify**

1. Different sources of variation.
2. Measure the contribution of each identified variable.
3. Isolate specific observation of primary interest.

- **Types of Statistical Tests**

1. *t*-test of significance.
2. Chi-squared tests of significance.
3. Analysis of Variance (ANOVA).

ANOVA

- Based on certain assumptions.

1. Subjects should be ***randomly*** subjected to the sequences of the study.
2. ***Variances*** associated with the 2 treatments as well as between sequence groups should be equal or at least comparable.
3. ***No interaction*** between subject, treatment, sequence and period.
4. Data obtained from bioequivalence studies should be ***normal***.

t-test of significance

- Determines significance of difference observed between experimental conditions and control.

1. Two Independent sample t-test

Used to compare 2 samples to check whether they are drawn from the same population.

2. Paired t-test

Used when two different treatments are given to a single group of experimental units.

- E.g. 1. test and std are given to the same subjects on different occasion.
  2. Comparison of new analytical method with already existing method.

Chi squared test of significance

- Can assume many different forms.
- 1. Checks agreement between expected frequencies and observed frequencies

-Chi square (X_2) is a probability distribution derived from the sum of squares of chi square statistic and if the calculated value exceeds the value in table, difference is significant.

- E. g Tossing of coin

2. To check whether a new drug is effective in preventing death of animals due to a specific disease.

- For bioequivalence testing two products can be considered bioequivalent ***if 90% confidence interval of the ratio of untransformed pharmacokinetic parameters for test and reference (T/R) lie within the range of 80% – 120%.***

- Products are bioequivalent if relative difference in the parameters is in the range of +/- 20%.

Statistical analysis

- BE criteria

-Two one-sides tests procedure

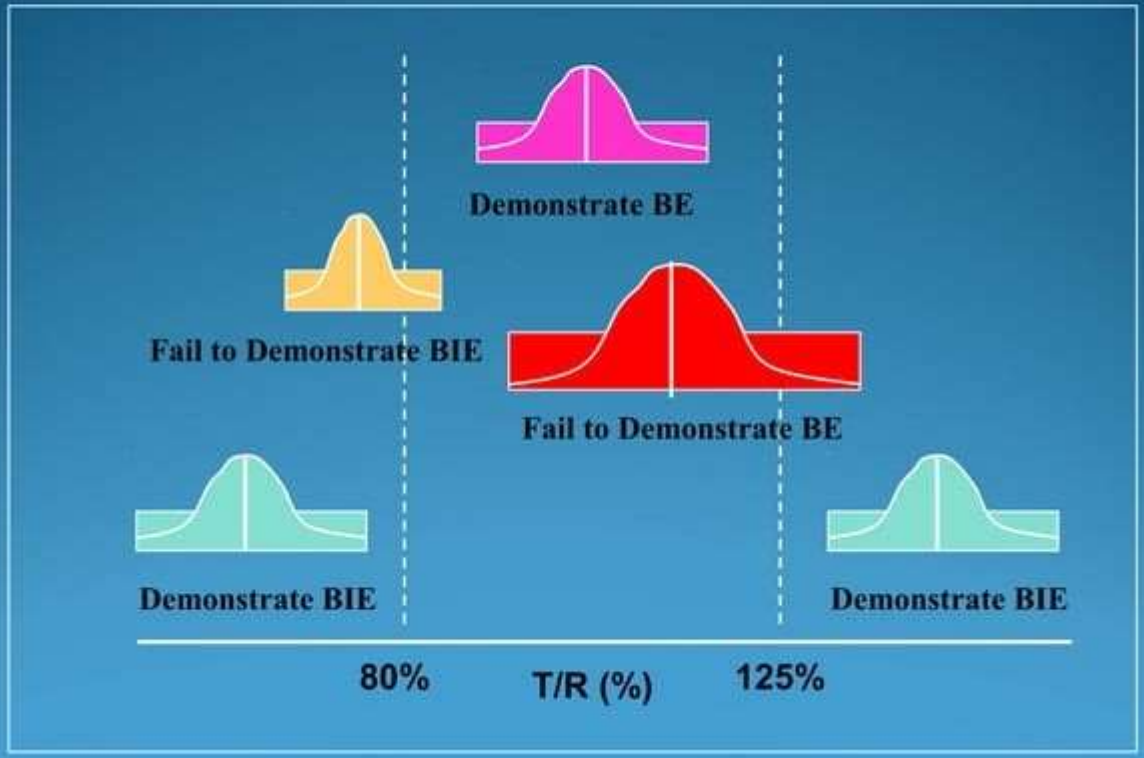
Test (T) is not significantly less than reference

Reference (R) is not significantly less than test

Significant difference is 20% ($\alpha = 0.05$ significance level)

T/R = 80/100 = 80%, or 100/80 =125%

BE Results (90% CI)



BIOEQUIVALENCE LIMITS

- The concept of ± 20% difference is the basis of BE limits.
- If the concentration dependent data were linear, the BE limits are 80-120%.
- On the log scale, the BE limits are 80-125%.
- Log transformed Cmax and AUC data are analysed by ANOVA.
- 90% CI interval of the geometric mean ratio of Test and Reference products must fall within the specified limits of 80-125% for products to be considered

9. Drug accountability

10. Appendix

WHY DO BE STUDIES FAIL ?

- Bioinequivalent products
- Not sufficient subjects/power (highly variable drug products)
- Highly variable formulations
- Problems with the bioanalytical method
- Are the volunteers really healthy ?
- Clinical logistics – unit dose preparation (e.g., suspension), timely sample collection, water availability, meal standardization, concomitant medication, etc.

THE INDIAN SCENARIO….

DRUG REGULATORY AUTHORITY OF INDIA

Ministry of Health & Family Welfare

- The Drug Controller General of India (DCGI)

The Food and Cosmetics Act, 1940;
Drugs & Cosmetics Rules, 1945;
Drugs & Cosmetics (II[nd]) Rules, 2005.

Schedule 'Y'
(Requirements and guidelines for permission to import and/or manufacture new drugs for sale to undertake clinical trials)

GUIDING DOCUMENTS

- Guidelines for Bioavailability and Bioequivalence Studies (DRAFT) CDSCO, Version 8, November 17, 2003.

To be followed in conjunction with ...

- Schedule 'Y' (Revised 2005)
  Requirements and guidelines for permission to import and/ or manufacture new drugs for sale or to undertake clinical trials

- Indian Good Clinical Practices
  CDSCO, December 2001.

- Ethical Guidelines for Biomedical Research on Human

WHEN IS A BE STUDY NEEDED IN INDIA ?

- A new drug is launched in India for the first time
  - The first applicant conducts a clinical trial and a BA study
- For the first four years or until inclusion in the Indian Pharmacopoeia
  - All the applicants conduct BA studies
- After four years
  - BA study not required.

FDA's Bioequivalence Hearing (1986)

- "..seems sensible to think that swallowing something that turns into a solution rapidly would be difficult to lead to differences from one product to the next....."
  - Bob Temple in response to Arnold Becketts presentation

- "....I've learned that there is no support here for attempting to provide such assurance solely with in vitro data."
  - Milo Gibaldi

BCS-Based Biowaiver to *In Vivo* Bioavailability/Bioequivalence Studies

According to BCS, *in vivo* bioavailability and bioequivalence studies need not be conducted for drug products under following circumstances -

- Rapid and similar dissolution.
- High solubility.
- High permeability.
- Wide therapeutic window.
- Excipients used in dosage form are same as those present in approved drug product.

- The drug product is a solution intended solely for intravenous administration, and contains the active drug ingredient in the same solvent and concentration as an intravenous solution that is the subject of an approved full New Drug Application (NDA).

- The drug product is a topically applied preparation intended for local therapeutic effect.

- The drug product is an oral dosage form that is not intended to be absorbed, e.g., an antacid.

- The drug product is administered by inhalation and contains the active drug ingredient in the same dosage form as a drug product that is the subject of an approved full NDA.

- The drug product is an oral solution, elixir, syrup, tincture or other similar soluble form that contains an active drug ingredient in the same concentration as a drug product that is the subject of an approved full NDA and contains no inactive ingredient that is known to significantly affect absorption of the active drug ingredient.

- The drug product is a solid oral dosage form (other than enteric-coated or controlled-release) that has been determined to be effective for at least one indication in a Drug Efficacy Study Implementation (DESI) notice and is not included in the FDA list of drugs for which *in vivo* bioequivalence testing is required.

Methods for enhancement of Bioavailability

- Pharmaceutic Approach
- Pharmacokinetic Approach :
- Biologic Approach

Pharmaceutical Approach:

- It involves modification of --formulations, manufacturing process or the physicochemical properties of drug without changing the chemical structure.
- Mainly aimed at **enhancement of dissolution rate** (**rate limiting step**).

Pharmacokinetic approach :

- Modification of chemical structure .

Biologic approach :

- Changes in the routes of administration.

Methods to increase effective surface area :

- **Micronization**.

  Methods:
  - spray drying
  - air attrition methods.

  E.g. : Aspirin
  Griseofulvin
  Steroidal compounds
  Sulfa drugs

- **Use of surfactants** :
  1. 'Surfactants promote wetting & penetration of fluids into solid drug particles.'
  2. Better membrane contact.
  3. Enhanced membrane permeability.
  -
  - Surfactants are used below CMC(critical micelle concentration)
  - E.g. Spironolactone

- **Use of salt forms**:

  E.g. Alkali metal salts of acidic drugs like penicillins
  Strong Acid salt of basic drugs like atropine.

- **Alteration of pH of drug microenvironment:**
  i. In situ salt formation
  ii. Buffered formulation e.g. Aspirin

- **Use of Metastable Polymorphs :**
  - more stable than stable polymorph

  e.g. Chloramphenicol palmitate .

- **Solute-solvent complexation**:

  - Solvates of drugs with organic solvents (pseudo polymorphs) have higher aqueous solubility than their respective hydrates or original drug .

  E.g. 1:2 Griseofulvin – Benzene solvate.

- **Selective adsorption on insoluble carriers :**

  - A highly active adsorbent like inorganic clay e.g. Bentonite, enhance dissolution rate by maintaining concentration gradient at its maximum.

  E.g. Griseofulvin
  Indomethacin
  Prednisone.

- **Solid solution(Molecular dispersion/mixed crystals)** :

  - It is a binary system comprising of solid solute molecularly dispersed in a solid solvent.
  - Systems prepared by Fusion method : **Melts**
  - e.g. Griseofulvin-succinic acid

- **Solid dispersions (Co evaporators/co precipitates)** :

  - Both the solute and solid carrier solvent dissolved in common volatile liquid e.g. Alcohol
  - The drug is precipitated out in an amorphous form as compared to crystalline forms in solid solutions/eutectics.

  E.g. Amorphous sulfathiazole in crystalline urea.

Eutectic mixture :

-It is intimately blended physical mixture of two crystalline components.

- Paracetamol -urea
- Griseofulvin – urea
- Griseofulvin-succinic acid

- Disadvantage :

  Not useful in :

  a) Drugs which fail to crystallize from mixed melt.
  b) Thermo labile drugs
  c) Carrier like succinic acid decompose at their melting point.

- **Molecular encapsulation with Cyclodextrins** :

-β and γ Cyclodextrins have ability to form inclusion complexes with hydrophobic drug having poor aqueous solubility.

- These molecules have inside hydrophobic cavity to accommodate lipophilic drug , outside is hydrophilic.

E.g. Thiazide diuretics

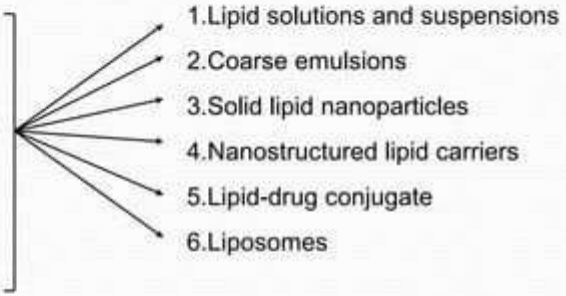
Barbiturates

Benzodiazepines

NSAIDS.

Bioavailability enhancement through enhancement of drug permeabiliy across biomembrane

- Lipid technologies



- Ion pairing
- Penetration enhancers

Bioavailability enhancement through enhancement of drug stability

- Enteric coating
- Complexation
- Use of metabolism inhibitors

Bioadhesive delivery system

Controlled release microencapsulated system

Immobilisation of enzyme inhibitors

Bioavailability enhancement through gastrointestinal retention

- Increased contact with epithelial surface
- Prolonging residence time in the stomach
- Delaying intestinal transit

INTERNATIONAL GUIDELINES FOR BE STUDIES

Guidance	Agency / Country	Link
Guidance for industry Bioavailability and Bioequivalence Studies for orally administered drug products - General considerations	US FDA	http://www.fda.gov/cder/guidance/4964dft.htm
Guidance for industry Conduct and Analysis of Bioavailability and Bioequivalence Studies- Part B: Oral Modified Release formulations	Canada	http://www.hc-sc.gc.ca/hpfb-dgpsa/tp
Recommended Guidelines for Organizations such as Contract Research Organizations (CROs) performing Bioequivalence studies on behalf of sponsors	WHO	http://mednet3.who.int/prequal/GCP/QAS_120_GCP_Bioequiv_studies.pdf
Note for guidance on the investigation of bioavailability and bioequivalence	EMEA	http://www.emea.eu.int/pdfs/human/ewp/140198en.pdf

Topic –
In Vitro Drug Dissolution Model

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CONTENTS

BCS Classification

- It is a system to differentiate the drugs on the basis of their solubility and permeability.
- The drug substances are classified as:
  - Class I - High permeability, High solubility. Ex:- Metoprolol.
  - Class II - High permeability, Low solubility. Ex:- Ezetimibe.
  - Class III - Low permeability, High solubility. Ex:- Cimetidine.
  - Class IV - Low permeability, Low solubility. Ex:- Hydrochlorothiazide

DISSOLUTION

- A process in which a solid substance is solubilised in a given solvent i.e., mass transfer from solid surface to liquid phase. (i.e., from solid to liquid)

(or)

- It is a process by which drug released from solid dosage form and immediately goes into molecular solution.

- It is a ***Rate Determining Step***

- If the drug is hydrophilic with high aqueous solubility then dissolution is rapid and rate determining step in the absorption of such drugs is rate of permeation through the bio membrane.

Absorption of such drugs is said to be

permeation rate limited* or *Tran's membrane rate limited.

Dissolution process of solid dosage Forms :

Theroies of Dissolution

1. Diffusion Layer Model/ Film theory
2. Danckwerts's Model/ Penetration or Surface Renewal Theory
3. Interfacial Barrier Model/ Double Barrier Theory

Diffusion Layer Model/ Film theroy

- Solution of the solid to form a thin layer at the solid/liq. interface is called ***Stagnant film or Diffusion layer*** which is with saturated drug.
- This step is Rapid
- Soluble solute form diffuses from the stagnant layer to the bulk of the solution. This step is slower and rate-determining step in drug dissolution.
- This rate of dissolution if the process is diffusion controlled and invovles no chemical reaction. It can be explained by ***Noyes – Whitney Equation .***

$$dC/dt = k(Cs-Cb)$$

where

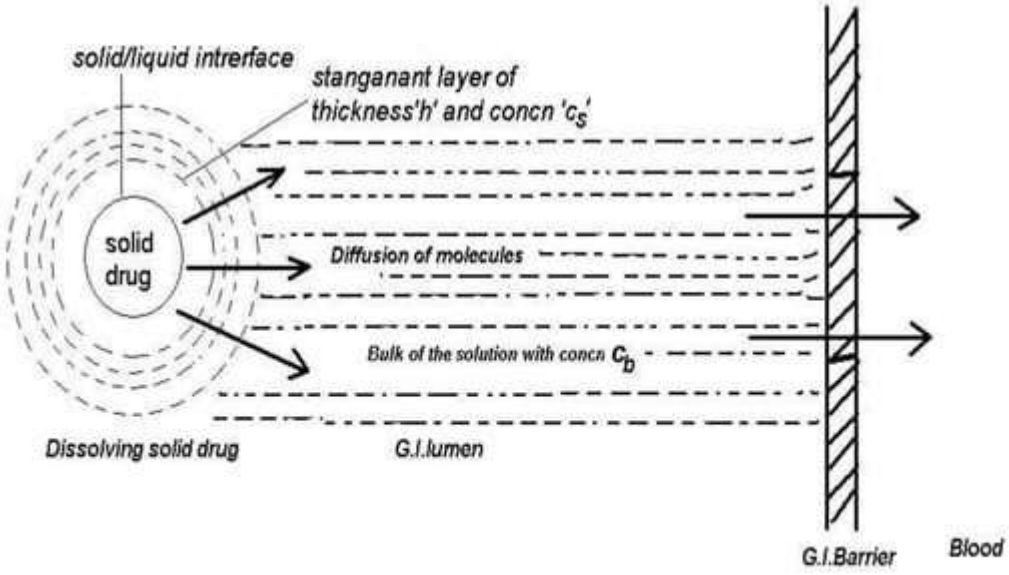
dC/dt = dissolution rate of drug

Cs = conc. Of drug in stagnant layer

Cb= conc. Of drug in bulk of the solution at time t.

k = dissolution rate constant. (First order)

Diffusion Layer Model/ Film theroy



Modified Noyes – Whitney Equation

$$dC/dt = \frac{DAK_{w/o}(Cs - Cb)}{h}$$

Where D= Diffusion coefficient of the drug

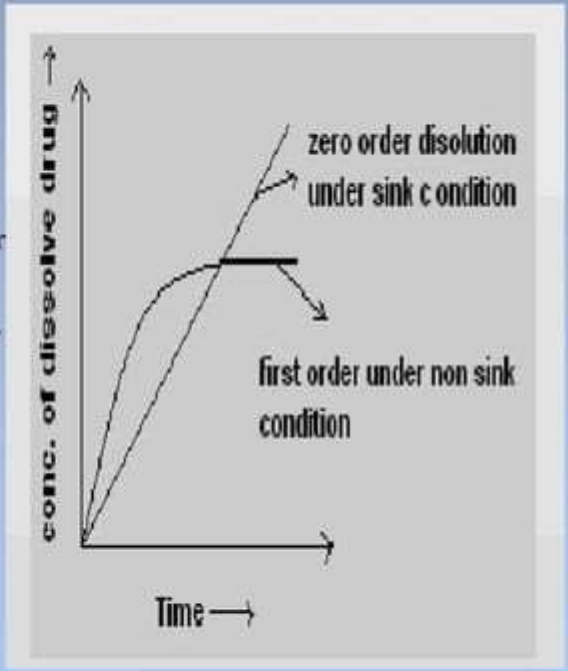
A = surface area of dissolving solid

$K_{w/o}$ = W/O partition coefficier of drug

V= Vol. of dissolution medium

h = thickness of stagnant layer

(Cs - Cb)= conc. Gradient for diffusion of drug .



Hixon and Crowell's Cubic root law of dissolution

$$W_0^{(1/3)} - W^{1/3} = K$$

W_0 = original mass of drug

W = mass of drug remaining to dissolve at time t

K = dissolution rate constant

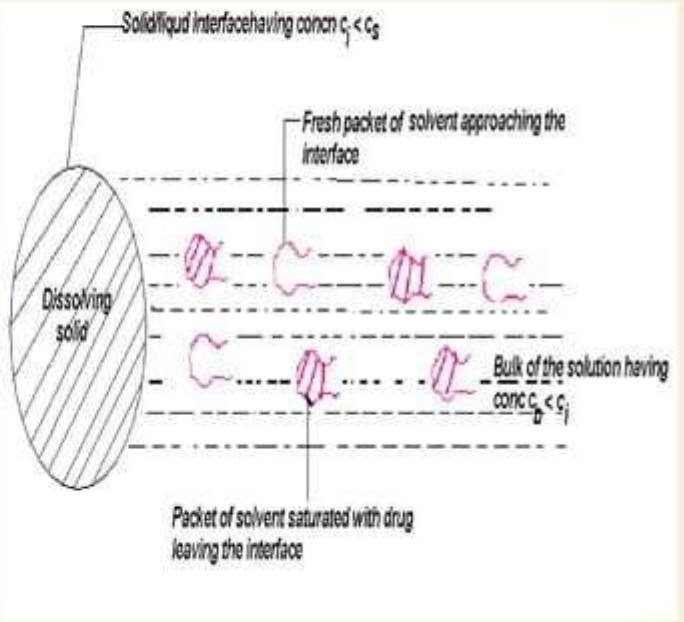
Danckwert's Model

- This model suggest that turbulence in dissolution medium

exists at the solid/liquid interface.

- As a result, agitated fluid consisting of macroscopic mass of eddies or packets reach the interface in random fashion due to eddy currents, absorb the solute by diffusion and carry it to bulk of the solution.
- Such solute containing packets are continously replaced with new packets of fresh solvent due to which drug conc. At S/L interface never reaches Cs and has lower limiting value of C_i
- This theory is also called as ***Surface Renewal Theory.***

Vdc/dt=dm/dt=A(cs-cb).√¥D



Interfacial Barrier Model

- According to the interfacial barrier model:
  An intermediate concentration can exist at the interface as result of solvation mechanism and function of solubility rather than diffusion. When considering the dissolution of a crystal, each face of the crystal will have a different interfacial barrier such a concept is given by the following equn.

$$G = K_i (c_s - c_b)$$

where

- G= dissolution rate per unit area.
  K_i =effective interfacial transport constant.
- Cs = Concentration of drug in the stagnant layer
- Cb =Concentration of drug in the bulk of the solution at time t

- In this theory, the diffusivity D may not be independent of saturation concentration cs. Therefore the interfacial model can be extended to both diffusion layer model and Danckwerts model.

IN-VITRO DISSOLUTION TESTING

- Dissolution and drug release tests are in-vitro tests that measure the rate and extent of dissolution or release of the drug substance from a drug product, usually aq.medium under specified conditions.
- It is an important QC procedure for the drug product and linked to product performance in-vivo.

❖ NEED FOR DISSOLUTION TESTING:

- Evaluation of bioavailability.
- Batch to batch drug release uniformity.
- Development of more efficacious and therapeutically optical dosage forms.
- Ensures quality and stability of the product.
- Product development, quality control, research and application.

IN-VITRO DISSOLUTION TESTING MODELS
Non-Sink methods

- **1) NATURAL CONVECTION NON SINK METHODS:**
  - a) Klein solvmeter method
  - b) Nelson hanging pellet method
  - c) Levy static disk method

- **2) FORCED CONVECTION NON SINK METHODS:**
  - a) Tumbling method
  - b) Levy or Beaker method
  - c) Rotating disk method
  - d) Particle size method
  - e) USP Rotating basket apparatus
  - f) USP Paddle apparatus

Sink methods

- **3) FORCED CONVECTION SINK DEVICES:**
  - a) Wurster pollis adsorption method
  - b) Partition method
  - c) Dialysis method s
  - d) Rotating disk apparatus

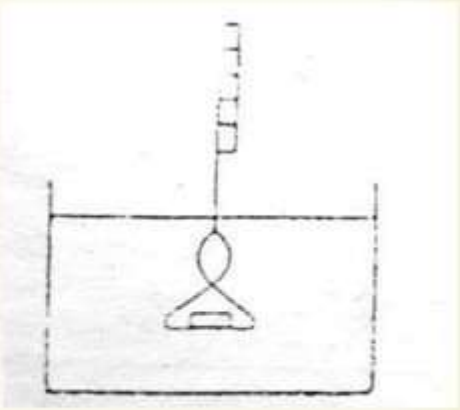
- **4) CONTINOUS FLOW/FLOW THROUGH METHODS:**
  - a) Pernarowski method
  - b) Langenbucher method
  - c) Baun and Walker
  - d) Tingstad and Reigelman
  - e) Modified column apparatus
  - f) Takenaka method

NATURAL CONVECTION NONSINK METHOD

'In this method the density difference is utilized for replacing the surrounding dissolution medium'

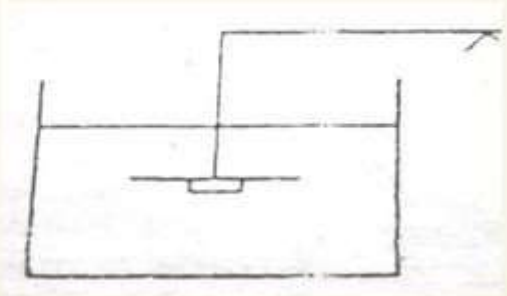
Klein Solvmeter method

- Carrier device surrounded by flat and is immersed in dissolution medium
- When dosage form is placed in the boat the bar moves and as dosage form dissolves it moves upwards
- Amount of dosage form dissolved is revealed from the difference in height of bar movement



Nelson hanging pellet method :

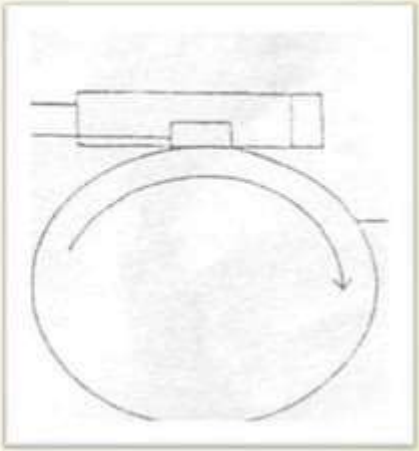
- Aluminum strip having provision for holding dosage form which is in turn connected perfectly maintained balance arm of strip
- Dosage form is mounted on aluminium strip with help of wax .this method can be employed to know Intrinsic dissolution rate.
- To prevent disintegration further high pressures can be applied and also constant surface .



Levy static Disk method

- Acrylic holder containing dosage form is inserted into a known volume of medium through rubber stopper
- The vial is inverted and placed in incubator at 37 C .At specific time intervals the vial is removed from incubator and samples are analysed
- Disadvantages :- effect of conc. On dissolution medium is ignored and the surface area of dosage form while dissolving is assumed constant which is not impractical.

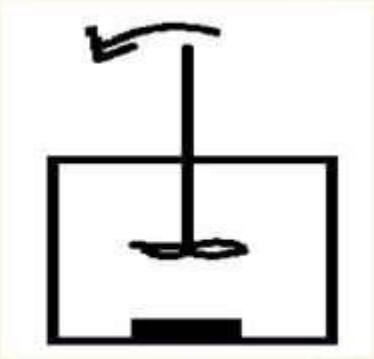
a. Tumbling Method:



- The Drug/ Dosage form with the dissolution medium is placed in test tube that is in turn clamped to the revolving drum which is rotated at the speed of 6-12rpm in water bath at 37 C
- The test tubes are removed and the medium is assayed at regular time points for the dissolved drug amount

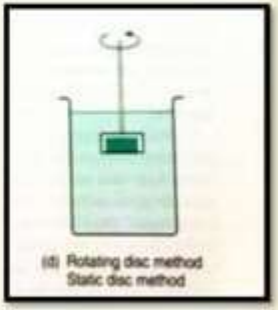
b. Beaker method

- Reported by Levy and Hayes(1960).
- Dissolution medium, 250ml of 0.1N HCl at 37°C placed
- in a 400ml beaker.
- Agitation by three blade polyethylene stirrer,5cm diameter and rotates at 60 rpm.
- Stirrer immersed to a depth of 2.7 cm in medium and in the center.
- Tablets are placed in a beaker and test was carried out.
- Samples are removed and assayed for the content.



c. Rotating disk method

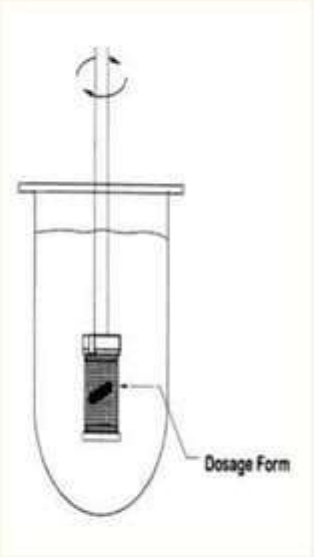
- Developed by late Eino nelson and described by Levy and Sahli.
- In this method ,the drug is compressed in a non-disintegrating disc without excipients.
- The disc is mounted in a holder so that only one face of the disc is exposed to the dissolution medium.
- The holder and disc are immersed in medium and held in a fixed position as in static disc method and rotated at a given speed in rotating disc method.
- Samples are collected at predetermined times.
- Surface area of the drug through which dissolution occurs is kept constant –intrinsic dissolution rate.



d. USP ROTATING BASKET

❖ **DESIGN:**

- Vessel: -Made of borosilicate glass.
  -Semi hemispherical bottom
  -Capacity 1000ml
- Shaft : -Stainless steel 316
  -Rotates smoothly without significance wobble(100 rpm)
  -Speed regulator
- Water bath:-Maintained at 37±0.5°C



❖ **USE**: Tablets, capsules, delayed release suppositories, floating dosage forms.

❖ Advantages

- ➢ Full pH change during the test
- ➢ Can be easily automated which is important for routine investigations.

❖ Disadvantages

- ➢ Basket screen is clogged with gummy particles.
- ➢ Hydrodynamic „dead zone“ under the basket
- ➢ Degassing is particularly important
- ➢ Mesh gets corroded by HCl solution.

e. USP paddle apparatus

❖ **DESIGN:**

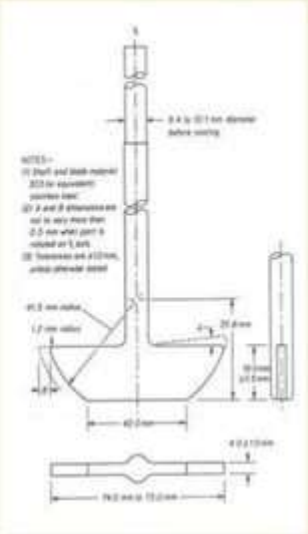
- Vessel: -Same as basket apparatus
- Shaft: -The blade passes through the shaft so that the bottom of the blade fuses with bottom of the shaft.
- Stirring elements: **-Made of teflon**

  For laboratory purpose

  -Stainless steel 316
- Water-bath: -Maintains at 37±0.5°C
- Sinkers : -Platinum wire used to prevent tablet/capsule from floating

❖ Advantages

- Easy to use
- Robust
- pH change possible
- Can be easily automated which is important for routine investigations



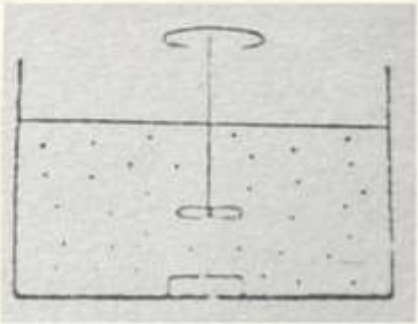
❖ Disadvantages

- pH/media change is often difficult
- Hydrodynamics are complex, they vary with site of the dosage form in the vessel (sticking,floating) and therefore may significantly affect drug dissolution
- Sinkers for floating dosage forms

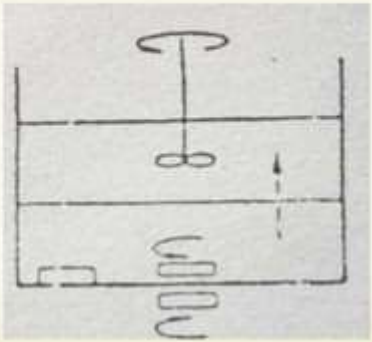
Forced Convection Sink Devices:

An ideal dissolution process is one which will mimic the invivo conditions by maintaining perfect sink conditions. these perfect sink conditions can be maintained by either of the following systems:

a) Fixed fluid volume.
b) Multiple phase
c) Continuous fluid flow



A. *Wurster-Polli Adsorption Method*:
In this method the dissolved drug is adsorbed by charcoal or bentonite.
care should be taken regarding the adsorbent, adsorbent should not alter the viscosity of the medium



B. *Partition Method:*
In this device organic phase is employed to remove the dissolved drug such that the drug would partition between the lipophilic and hydrophilic phases.
selection of organic phase plays a critical role.

C. *Dialysis Method:*

- Cell consist of 32mm inflated membrane.
- Plugged at the lower end by tight fitting cylindrical perspex box.
- Upper end of the tube held by thin perspex ring inserted into the tube and secured by an elastic band.
- The cell suspended , from the arm of the tablet disintegration apparatus and containing the dosage form in 150ml of distilled water at 37°C.
- The cell is raised or lowered 30times a min, into 150ml of distilled water at same temperature.
- Agitation by slight flexing and stretching of the dialysis membrane as it enters and leaves the bath. Rotated at 60rpm.

.

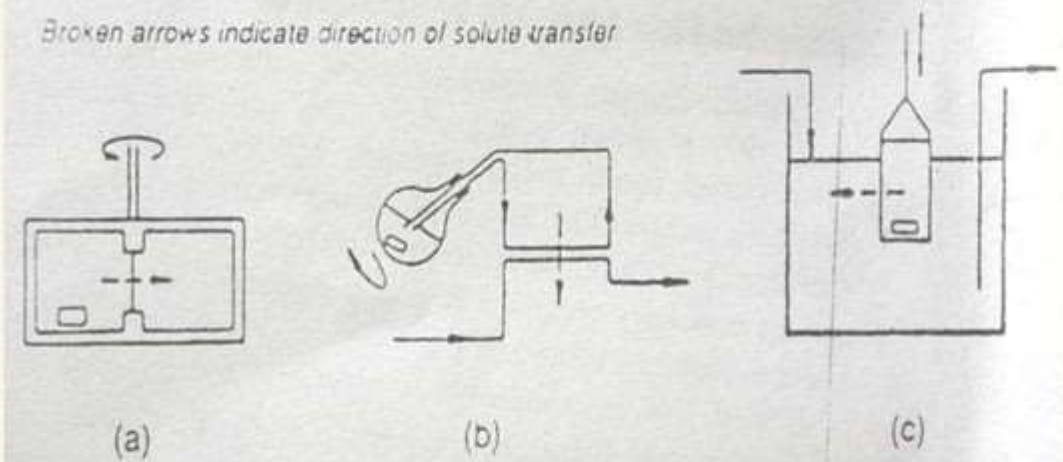


Fig. 3.16 Schematic illustration of a forced-convection sink dissolution testing method: dialysis devices using (a) rotating cell, (b) rotating flask and external dialysis, and (c) oscillating cell

D. **Rotating Flask apparatus:**

- In this method a flask containing dissolution medium is rotated around its horizontal axis in a water bath kept at a temperature of 37 C.
- The flask has a provision of sampling such that aliquots can be withdrawn and the fresh medium can be replaced back.
- This apparatus is best suited for oral solid dosage forms like tablets and capsules since they do not require much agitation.

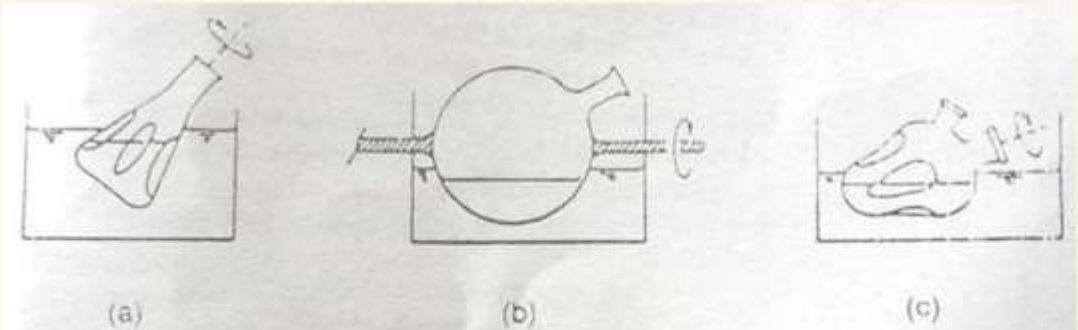


Fig. 3.17 Schematic illustration of a forced-convection sink dissolution testing method: rotating flask devices by (a) Ferrari and Khoury, (b) Gibaldi and Weintraub, and (c) Koch

Flow Through Devices

For the drugs which saturate rapidly in large volumes of medium, USP apparatus will not serve the purpose.

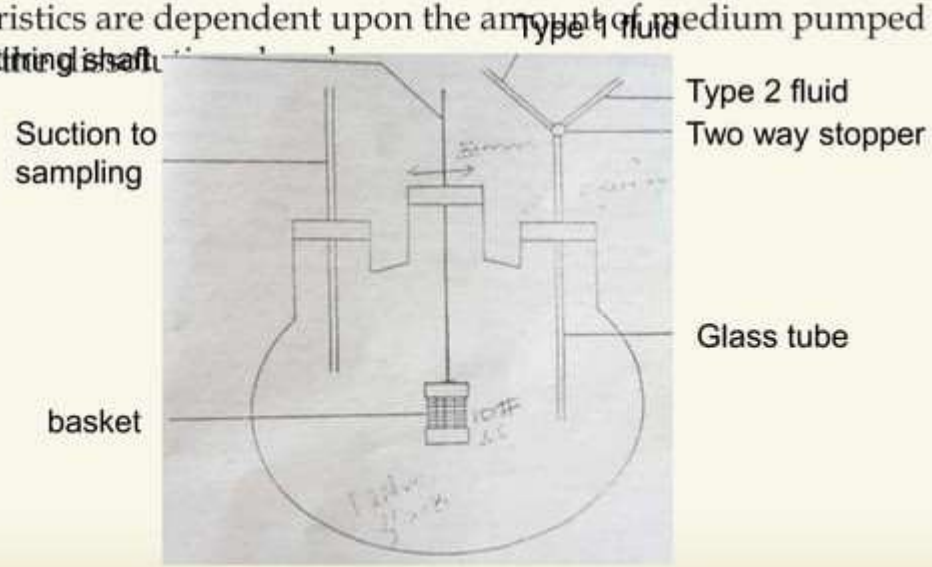
- For this the suitable device is flow through device. In this device unlimited quantity of fresh dissolution is available.
- A dosage form is placed in a small cell and is subjected to a stream of fresh dissolution media.

4. CONTINUOUS FLOW APPARATUS BY PERNAROWSKI

:

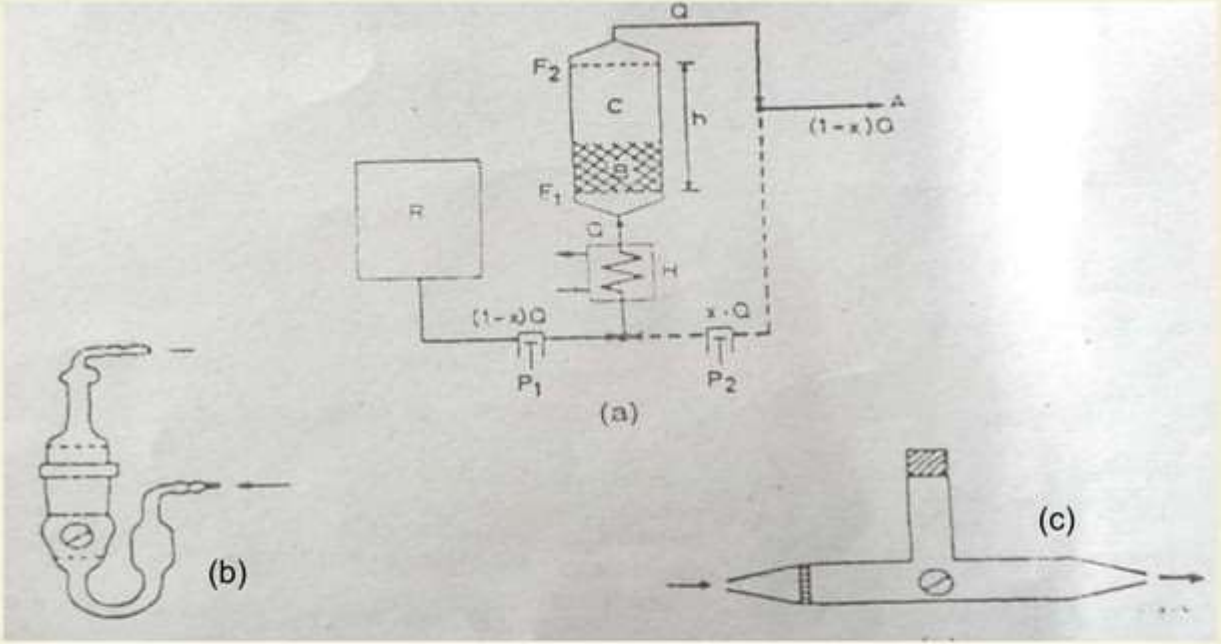
It consists of 10 mesh stainless steel basket stirrer assembly with an adjustable stirrer.

- the chamber is 3 necked flask of 33 mm and the rest two of 20 mm diameter.
- 1L of medium is employed within the flask. the dissolution characteristics are dependent upon the amount of medium pumped through the flask.



B. LANGENBUCHER COLUMN-TYPE FLOW THROUGH METHOD:

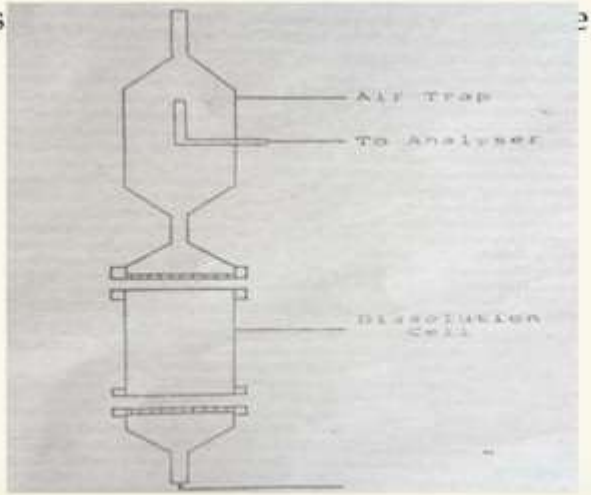
- This device is according to the dissolution basic design .
- The screen is constructed such that the medium flows equally through the entire cross section in a laminar pattern.
- This is again closed by a secondary screen, filter which prevents the undissolved drug from being eluted.



(a) B-particle bed, C-cell, F1&F2-screens, H-heat exchanger, h-height of the cell, P1,P2-volumetric pumps, R-liquid reservoir, x-circulatory factor, Q,xQ,(1-x)Q=volumetric flow rates,
(b) And (c) =designs of flow through cells

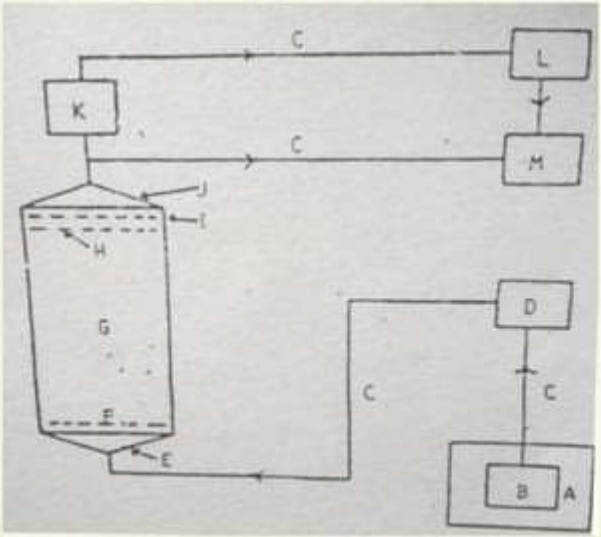
CONTINUOUS FLOW APPARATUS BY TINGSTAD AND RIEGELMAN:

- a cylindrical glass cell of 6.1 cm long and 1.9 cm in diameter constructed with two glass filter funnels is used.
- The dissolution cell has filter membranes which prevents the solid particles from being analyzed.
- There are also external valves to control the excess flow of solvent into the system. the air trap averts air bubbles.
- The complete as e bath kept at 37 C.



FLOW-THROUGH MODIFIED COLUMN APPARATUS:

- The device consists of filter of 14 M -size made of nylon.
- the tubing from the pump is connected to the dissolution cell.
- the Teflon faced stainless steel supports the screen resting on the bottom half of the filter holder.
- The direction of the flow is such that the particles do not fall through the screen. the rest of the process is the same.



CONTINUOUS FLOW APPARATUS BY TAKENAKA

- The release of drug is measured with the aid of in vitro simulator device consisting of flow type dissolution container.
- The dosage form is placed in the basket rotating at 94 rpm with 300 ml of medium.
- then the medium is removed by collecting reservior using peristaltic pump.
- aliquots are withdrawn using syringe and then filtered using Whatman filter paper and the same volume is replaced immediately with fresh medium.

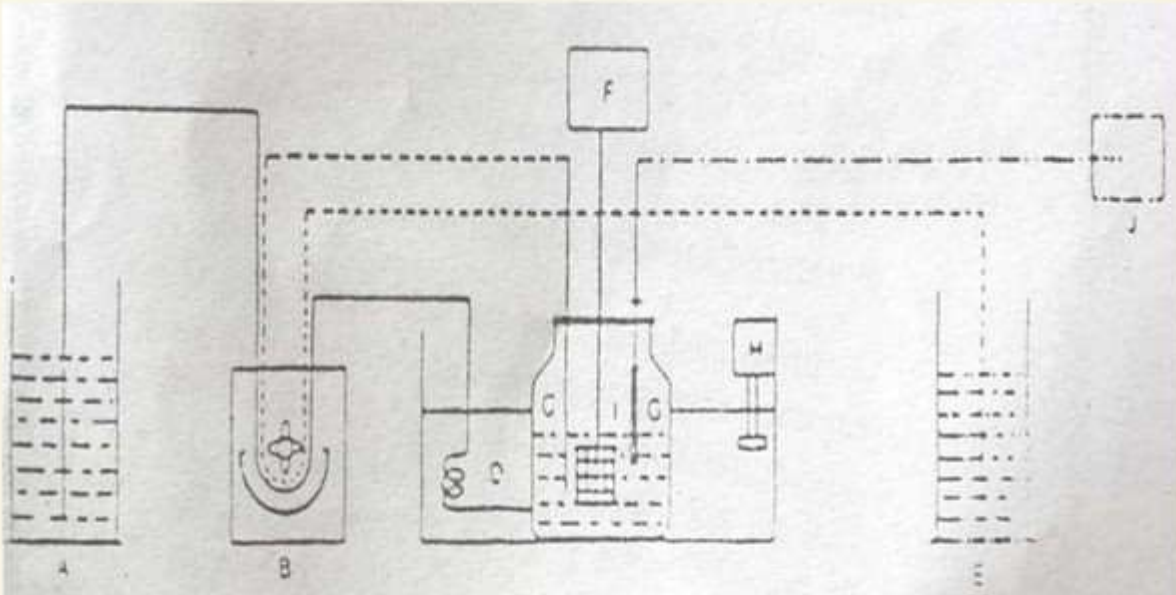


Fig. 3.25 Schematic illustration of a flow-through dissolution testing system (Tanaka et al. A, Simulated intestinal fluid reservoir; B, peristaltic pump; C, dissolution container; D, water bath; E, collecting reservoir; F, motor; G, pH electrodes; H, th r

FACTORS INFLUENCING DISSOLUTION AND DISSOLUTION STUDIES

1. Physicochemical Properties of Drug
2 .Factors Relating To Dosage Form

Physicochemical Properties of Drug

1) DRUG SOLUBILITY

- Solubility of drug plays a prime role in controlling its dissolution from dosage form.
- Minimum aqueous solubility of 1% is required to avoid potential solubility limited absorption problems.

2) PARTICLE SIZE:

- There is a direct relationship between surface area of drug and its dissolution rate.
- ***Absolute Surface area and Effective Surface area .***

3)POLYMORPHISM AND AMORPHISM:

- When a substance exists in more than one crystalline form, the different forms are designated as polymorphs and the phenomenon as Polymorphism

4)SOLVATES AND HYDRATES:

- ✓ The stoichiometric type of adducts where the solvent molecules are incorporated in the crystal lattice of the solid are called as ***solvates***
- ✓ The trapped solvent is called as ***solvent of crystallization***
- ✓ These solvates can exist in different crystalline forms called as pseudopolymorphs.
- ✓ When the solvent is water, the solvate is known as ***hydrate***
- ✓ Hydrates are most common solvate forms of the drugs.

5)SALT FORMATION

- It is one of the common approaches used to increase drug solubility and dissolution rate.
- Most drugs are either weak acids or weak bases
- Generally, for weakly acidic drugs, a strong base salt is prepared (Na and K salts of barbiturates and sulfonamides) whereas for weakly basic drugs, a strong acid salt is prepared (HCl or sulfate salts of alkaloidal drugs).

Factors relating to the dosage forms:

PHARMACEUTICAL EXCIPIENTS

1. **Vehicle** (*Ex: Propylene Glycol (Water Miscible Vehicle*)
2. **Binders** (*Ex. Ethylcellulose retard dissloution)*
3. **Disintegrants** (*Ex: MCC)*
4. **Lubricants**
5. **Colorants** (*Ex:Brilliant blue retards dissolution of sulfathiazole)*
6. **Surfactants** (*Ex: Tween80 with phenacetin*)
7. **Complexing agents** (*Ex: hydroquinone-digoxin complex)*
8. **Crystal growth inhibitors** (*Ex: PEG, PVP)*

CONCLUSION:

- By studying various factors influencing the rate of dissolution, we can optimize the different properties of the formulation.
- By conducting dissolution studies we can know the batch to batch reproducibility.
- We can estimate the solubilty profiles of the drug.
- The best available tool today which can atleast quantitatively assure about the biological availability of drug from its formulation is its invitro dissolution.

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Thank you

Topic –
IVIVC - Concept

Presented By
Mr. Vishal V. Kalal
Ass. Prof.

JES'S College Of Pharmacy ,Nandurbar.

Learning objectives

Upon completion of presentation you will

- Understand the definition and concept of IVIVC.
- Clear concept of the objective of IVIVC
- Understand the approaches, level of IVIVC, application.

Definition

In vitro-in vivo correlation is defined as

- *predictive mathematical model*
- *that describes the relationship between*
- *an in-vitro property (such as the rate of dissolution) of a dosage form and*
- *an in-vivo response (such as the plasma drug concentration).*

Definition

"In vitro-in vivo correlation is defined as the predictive mathematical model that describes the relationship between an in-vitro property (such as the rate of dissolution) of a dosage form and an in-vivo response (such as the plasma drug concentration)."

Objectives/Significance of *ivivc*

- The main objective of developing and evaluating an IVIVC is to enable the dissolution test to serve as a surrogate. It reduces the number of bio-equivalence required for approval as well as during scale up and post approval changes (SUPAC).
- IVIVC shortens the drug development period, economizes the resources and leads to improved product quality.
- A means of assuring the bioavailability of active ingredients from a dosage form.
- Supports and or validates the use of dissolution methods and specifications.

Approaches

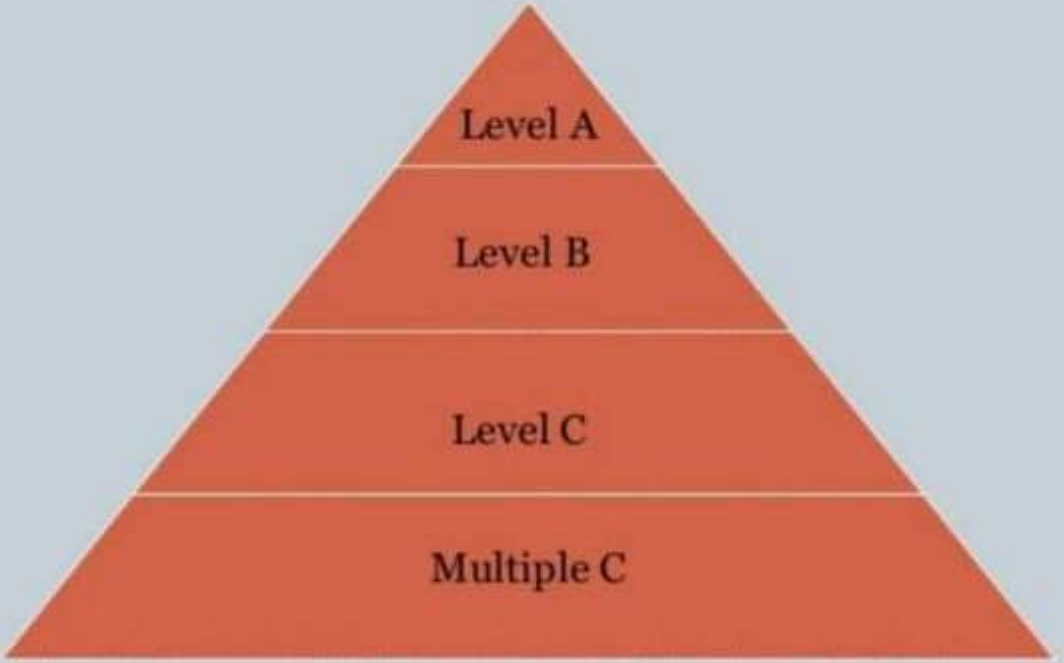
Two basic approaches

1. By establishing a relationship between the *in vitro dissolution and* the *in vivo bioavailability parameters*.
2. By using the data from previous bioavailability studies to modify the dissolution methodology in order to arrive at meaningful *in vitro-in vivo correlation*.

Parameters for Correlations

S. No.	*IN VITRO*	*IN VIVO*
1	Dissolution rate	Absorption rate (or absorption time)
2	Percent drug dissolved	Percent of drug absorbed
3	Percent drug dissolved	Maximum plasma concentration, Cmax
4	Percent drug dissolved	Serum drug concentration, Cp

Levels of Correlation



Level A Correlation

- Highest category of correlation.
- Linear correlation.
- Superimposable in vitro and in vivo input curve Or can be made superimposable by use of a constant offset value.
- Most informative and useful from a regulatory perspective.

Level B Correlation

- Uses the principles of statistical moment analysis
- The mean in vitro dissolution time is compared either to the mean residence time (MRT) or to the mean in vivo dissolution time.
- Is not a point-to-point correlation.
- Level B correlations are rarely seen in NDAs

Level C Correlation

- Level C correlation represents a single point correlation.
- One dissolution time point (t50%, t90%, etc.) is compared to one mean pharmacokinetic parameter such as AUC, tmax or Cmax.
- Weakest level of correlation as partial relationship between absorption and dissolution is established.

Multiple Level C Correlations

- Multiple Level C correlation relates one or several pharmacokinetic parameters of interest (Cmax, AUC, or any other suitable parameters) to the amount of drug dissolved at several time points of the dissolution profile.
- Its correlation is more meaningful than that of Level C as several time points are considered.

Applications

1. To ensure batch-to-batch consistency in the physiological performance of a drug product.

2. To serve as a tool in the development of a new dosage form.

3. To assist in validating or setting dissolution specifications.

Any doubt and question?

Thank you....