TERMINOLOGIES OF Biopharm.

- Pharmaceu. equivalent
- Bioequivale.
- Therap. equiv.
- Biosimi.
- ph. alternative
- chemical eq.
- Therap. alternative
- Biowaiver.

process of disp. ph Alter is know as pharmaceutical substitution.

★ - Pharm. EQUIV

✓ Drug product that contain same amount of identical API
- same salt, ester, chemical form.
- same dosage form
- strength, concen. route of adm.

✓ can be substituted

✓ NOT necessarily same API But most often same.

✓ comply ē same compendial (eg USP) requirements

Examp. Lisinopril 20mg Tab.

Pharm. Alternative

✓ contains same API But diff. salts or are avail in diff dosage forms.

✓ can't be substituted ēout approval from physician

✓ Examp:-
(1) • metoprolol succinate 100mg extended release.
• metoprolol tartrate 100mg immediate releas.
(2) Keflex (cephalexin monohyd)
• Capsules
• Tablets
(3) Tetracyc. HCl 250mg caps Y/S Tetracy. phosphate 250mg caps

Chemical EQUIVALENT:-

when 2 or more drug products contains same labelled chemical substance as an active ingr. in same amount.

e.g. • Dilantin capsule = phenytoin 100mg
susp = 30mg/5ml.
• epitoin Tab = phy 100mg, susp. 30mg/5ml

Panadol - 500mg paracea Disprol - paracea 500mg

★- **Bioequivalent:-** (includes) drug products that are pharmaceutical equivalent and have same/similar bioavailability when administered in same molar dose of API, in same chemical form, in similar dosage form. by the same route of admn. & under the same experimental condition

Example: Budeprion XL - 150mg (Bupropion)
v/s.
Wellbutrin XL - 150mg (Bupropion)
(Anti-depress)

★- **THerap. Alternative**

Drug products that contains
- different API
- indicated for same therapeutic or clinical objective

e.g.
Ibuprofen given instead of aspirin

Cimetidine instead of Ranitidine

Thera. equivar.

Drug product that are
- pharmac. equivar
- same clinical effect
- Same safety profile.
- identical amount of same API
- adequately labelled
- manf. acc. to CGMP.
- same dosage/route
- Bioequiv.

∴ T.E = phar. eq. + Bioeq.

Therapeutic Subs.

process of dispensing a Therap. alternative in place of prescribed drug product

e.g.
1) amoxicillin in place of ampicillin
2) Ibuprofen instead of naproxen.

- All approved drugs & their Theta. equi are mentioned in Orange BOOK by USFDA [CDER = center of drug evalu & research]. purple book is also a part of it.

BIOSIMILAR:- drug product that is highly similar to reference product notwithstanding minor difference in clinically inactive ingredients and no clinically meaningful differ. b/w biolog prod & ref. product in terms of safety, purity and potency.

- list is present in purple book.

e.g

Avsola (infliximab) — Remicade (infliximab)
(biosimilar name) reference prod.

BIOWAIVER:- This term is applied to regulatory drug approval process when dossier is approved based on evidence of equivalence, to other marketed product, other than invivo equivalence testing.

⇒ In 1995, American dept. of health & Human services, USFDA (HHS-FDA) instigated the Biopharmaceutical classif. system BCS & aim of granting so-called biowaiver for scale up and post-approval changes (SUPACs).

BIOAVAILABILITY:- rate & extent to which the active ingred. or active moiety is absorbed from drug product and become avail. at site of action

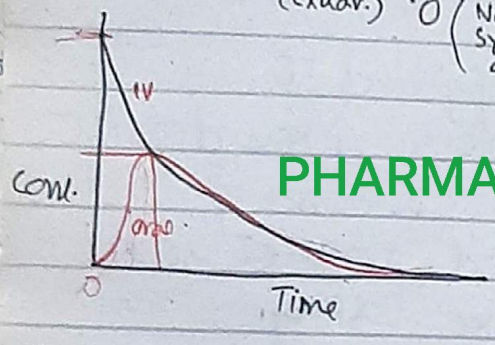
TYPES OF BIOAVAIL.

Absolute

comp bioavail of active drug in sys. circula. following extravascular adm ē bioaval of same drug following IV adm. (drug is consider 100% abs.)

$$F_{abs} = \frac{AUC_{po} \cdot Dose_{iv}}{AUC_{iv} \cdot Dose_{po}}$$

$F_{IV} = 1$, F_{abs} (extravas.) → 1 (100% sys. ab.) / 0 (NO Systemic abs.)



Relative

compare the bioavail of reference & test formulation of same drug.

$$F_{rel} = \frac{AUC_A \cdot D_B}{AUC_B \cdot D_A} \cdot 100$$

A = reference.

Method for Assessing bioavail & bioeq.

⇒ FDA's approaches for measuring in descending order.

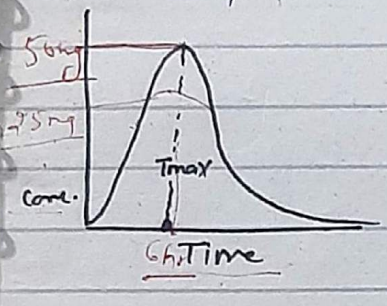
1) In-vivo measurement of active moiety or moieties in bio. fluid (ph-kinetic study).
2) In vivo - ph-dynamic study (response v/s time)
3) In vivo limited clinical comparison
4) In vitro comparison
5) Any other appr. deemed accep. by FDA.

IN-VIVO Measurement

*- PLASMA DRUG CONC.

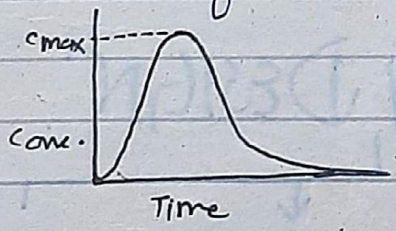
Tmax

- Time req. to reach max. drug conc. after adm.
- drug continue to abs. after tmax. but at slower rate
- unit = hours, min.
- most imp parameter for comparing delayed action products



Cmax

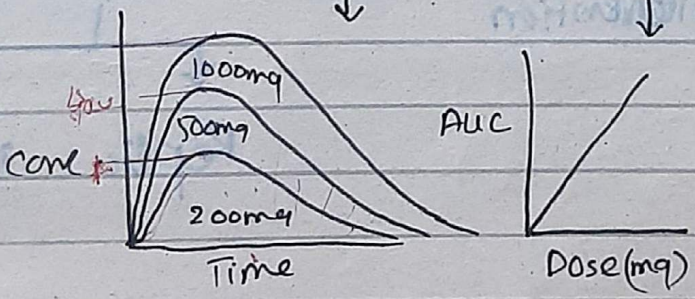
- represent max. plas. conc. obtained after oral adm. of drug.
- give indic. for therap response as well as for toxicity
- unit = mg/ml.
- large peak = more abs.
- small spike = small cmax; less abs.
- sometimes in bioeq. study, cmax indicate the rate of abs.



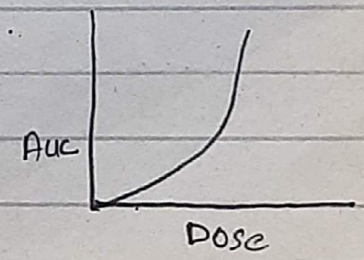
AUC

- Measurement of extent of drug bioavail
- AUC is a curve from $t=0$ to $t=\infty$
- $AUC = \frac{F D}{K V_D}$
- indepen. of route of adm. & elimi as long as elimin. process don't change
- Determin by Trapezoidal rule.
- unit = conc. x time
  ug. h / ml.
  Other units = wt & time/vol. Appear & large.

For some drugs, AUC is directly prop. to dose.



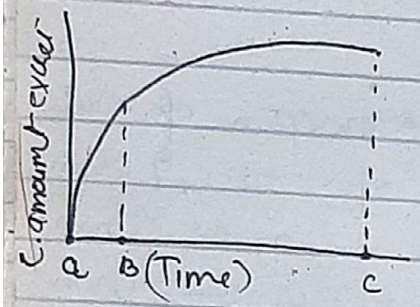
In some cases, AUC is not propo. to dose as sometime the pathway for elimi. become saturable

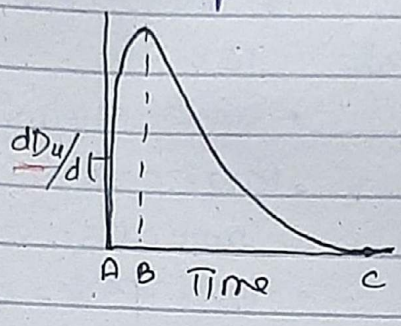


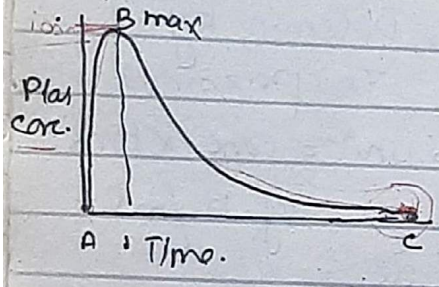
URINARY EXCRETION DATA

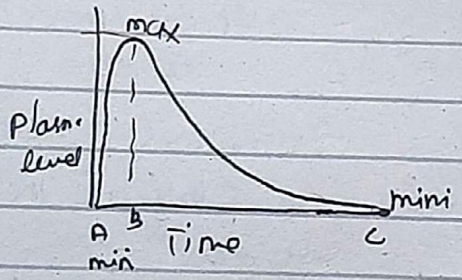
- indirect method
- Drug must be excr. unchan in signfi amount

Du^{∞}	dDu/dt	t^{∞}
• cumulative amount of drug excreted in urine • related directly to total amount of drug abs.	• Rate of drug excr. • Depend on first-order elimi. rate constant (k) & conc. in plasma cp.	• Total time for drug to be excreted • useful parameter in bioeq. studies









★-STUDY DESIGN

- Fasting
- Food intervention
- Parallel
- Cross-Over
  - Replic
  - Non-replic.

FASTING

Usually evaluated by
- Single dose
- Two period Two treatment
- Two sequence, open-label
- Randomized cross-over design
- comparing equal doses of Test & ref prod. in fasted, adult healthy subj.

★ - For immediate & modified release
★ Both male/Fe. can partic.
★ - Blood sample taken
★ Subj should be fasted overnight atleast 10hrs and continue fasting → 4hrs after dosing.
★ - No medi. for 1 week prior to study.

- parallel → for drug ē long $t_{1/2}$.
- Replic → for drugs ē high intra subj variability.

☐ period = time period in which a study is perfor.
∴ 2 period study = a study perf. on 2 diff. days separated by a WASHOUT PERIOD (10 $t_{1/2}$)

☐ Sequence: no. different orders in Treatment group
e.g 2 period 2 seq will be as

	Period 1 (21-Jan)	Period 2 (30-Jan)
Seq 1	T	R
Seq 2	R	T

T = Treatment / Test
R = Reference.

FOOD-INTERVENTION

Usual study Design uses:
- single dose.
- 2 period, 2 treatment
- randomized cross-over study Design.
- use for drugs affected by meal., involve using meal that affect GI physiology. [ibuprofen, naproxen]

★ Typical test meal (high-fat meal) (high-calori 800–1000 calories).
" 2 eggs fried in butter, 2 strips of bacon (salted-cured pork), 2 slices of toast ē butter, 4 oz. of brown potato and 8 oz of milk.

150 calories } protein
250 calories } carbo.
500–600 calories } fat.

★ - over night fast of 10hrs meal given 30min before dose, is consumed over 30min
★ Then immediately ē 240ml (8 fl) of water
★ - For modi + immediate rele. dosage forms.

DESIGNS

PARALLEL

for drug product having long elimination half-life.
e.g depot injections

- one group receive → Reference product
- one group receive → Test product

CROSS-OVER

In which each subject receive the test product as well as reference product

e.g Latin-square cross-over design for a bioequiv. study of 3 drugs in 6 volunteers

Drug product

Subj	peri 1	period 2	per 3
1	A	B	C
2	B	C	A
3	C	A	B
4	A	C	B
5	C	B	A
6	B	A	C

Replicated

1) For highly variable drugs
2) drug e Narrow TI

use to evaluate ein the subj variation for both test & reference.

" four period, 2 seq, 2 formulation is as.

	Period 1	2	3	4
seq 1	T	R	T	R
sequence 2	R	T	R	T

Non-replicated