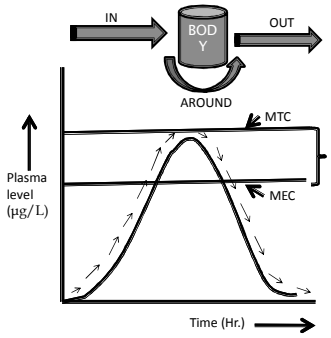
BIOAVAILABILITY

By
Dr. A. S. Adebayo

Bioavailability

- **The measure of rate and extent (total amount) of appearance, in general circulation, of pharmacological active form of an administered drug in a dosage form.**



$$Plasma\ Drug\ Level, C_p = \frac{Drug\ Dose, D_0}{Distribution\ Volume, V_p}$$

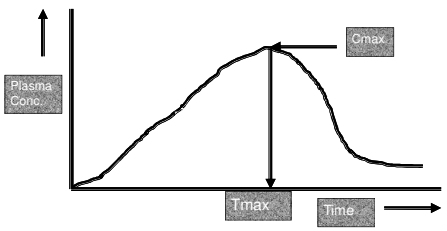
Factors Affecting Bioavailability of Drugs

- Physiological factors
- Formulation and manufacturing variables
- Physico-chemical properties of the active ingredients (drug).

Assessment of Bioavailability

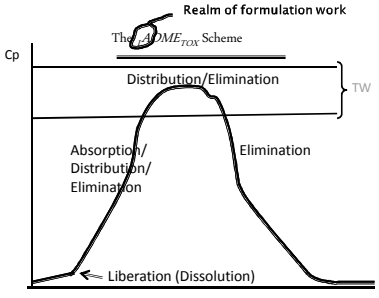
- **This could be done in two ways:**
- Single dose study
- Multiple dose study

Fig.1. Plasma conc. vs. time showing C_{max}

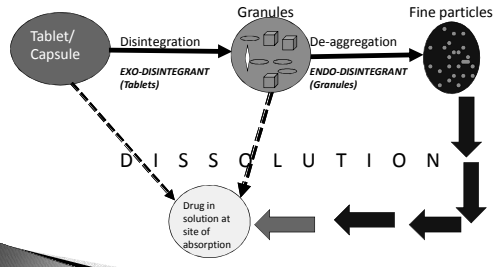


Dissolution-dependent Absorption

- For many drugs of low aqueous solubility, dissolution is rate limiting step in absorption
- BCS Classes 2 & 4 are the most critical



Tablet/Capsule Dissolution



Tuesday, February 08, 2011 7

Factors Affecting Bioavailability of Drugs

- PATIENT
  - Physiological factors
  - Patient conditions, route of administration, site of action
- PRODUCT
  - Formulation and manufacturing variables
  - Excipients, dosage form, process variables
- DRUG
  - Physico-chemical properties of the active ingredients (drug)
  - Chemical nature, solubility, permeability, dose size, crystalline properties

Tuesday, February 08, 2011 8

Bioavailabity parameters

- Absorption rate constant, *ka*
- C_{max} – Maximum concentration attained.
- T_{max} – Time to attain the maximum concentration.
- AUC – Area under the concentration–time curve

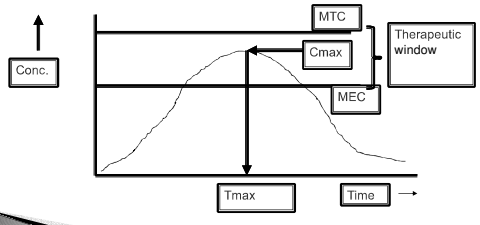
2/8/2011 9

Significance of Bioavailability parameters

- **Tmax is an index of the rate of bioavailability, i.e. the shorter the Tmax, the faster the absorption.**
- ***ka* is the absorption rate constant and a better index of bioavailability.**
- **Area Under the Curve (AUC) is a reflection of the extent or total amount of drug absorbed i.e. extent of bioavailability.**
- **Cmax helps us to know whether the maximum concentration attained leads to therapeutic effect or not.**

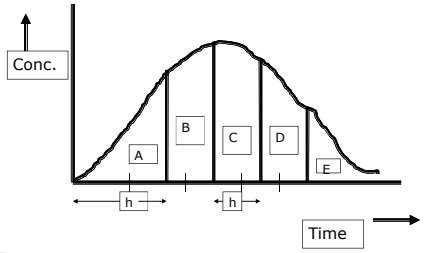
2/8/2011 10

Relationship between Cmax and therapeutic effect of drug



2/8/2011 11

AUC Measurement – Trapezoidal method of calculation



2/8/2011 12

AUC Measurement – Trapezoidal method of calculation

- **Area of each trapezoid = ½[the summation of parallel sides] x height.**
- **Generally, Trapezoidal eqn., is as:**

$$[AUC]_{tn-1}^{tn} = \frac{C_{n-1} + C_n}{2}(t_n - t_{n-1})$$

where C_n = concentration at time n, as applicable

AUC

- can be estimated from the last observed plasma conc. C_{pn} at t_n to time equal to infinity
- AUC total:

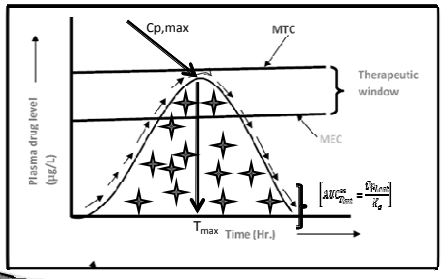
$$[AUC]_t^{\infty} = [AUC]_0^t + [AUC]_t^{\infty}$$

AUC Total = Extrapolated AUC + AUC0-t

Extrapolated AUC = C_{last}/kel

kel = elimination rate constant; C_{last} = conc. at time *t* i.e. the last conc

Drug Plasma level profile from oral absorption



39 42

DESIRED PARAMETERS

Parameters	PRODUCT A (AZC)	PRODUCT B (AZT)
Bioequivalence Factor, F†		
Relative Bioavailability‡	**Extent**	
$[AUC]_{Total}$ (ng.Hr.ml^{-1})*		
C_{max} (ng/ml)		
T_{max} (Hours)		
K_a (Hr^{-1})**	**RATE**	
K_{el} (Hr^{-1})		
$T_{1/2}$ (Hr.)**		

Absolute bioavailability (B_A)

$$B_A = \frac{AUC_{tab}}{AUC_{i.v}} X\,100\,\%$$

$$F = \frac{AUC_{oral}}{AUC_{iv}}$$

***F* is the fraction of the dose absorbed**

Relative bioavailability (B_R)

$$B_R = \frac{AUC_{test,oral}}{AUC_{std,oral}} X100\%$$

- Standard drug may or may not be the innovator product.
- Relative bioavailability is most commonly used in drugs not having injectable forms

Bioavailability data from urinary analysis

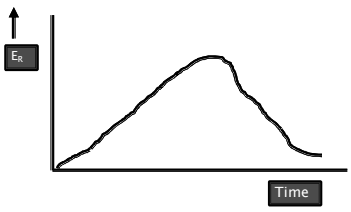
Time of collection (T_i)	Volume of urine (V)	Conc. of drug (C, from analysis)	Amount of drug (CxV)	Rate of excretion (CxV/T_i)	Cummulative amount excreted
0 – 1					
1 – 2					
2 – 4					
4 – 6					
6 – 8					

Rate of excretion:

$$\text{Rate of excretion (ER)} = \frac{\text{Amount of Drug}}{\text{Time interval}} mcg / Hr$$

$$E_R = A_E / T_i$$

Rate of excretion vs. time



Significance of t_{max} & D^{∞}_{U}

- Time for the maximum rate of excretion is an index of the rate of bioavailability
- The total cumulative amount of drug excreted in urine is an index of the extent of bioavailability.

Absolute & Relative Bioavailability from Urinary Data

$$B_A = \frac{D^{\infty}_{u,oral}}{D^{\infty}_{u,iv}} x100\%$$

$$B_R = \frac{D^{\infty}_{u,test\ (oral)}}{D^{\infty}_{u,std\ (oral)}}$$

Multiple Dose Study

- **Some conditions necessitate multiple dose study:**
  - If, following a single dose administration of a drug, the level of drug in the body cannot be detected by analytical process e.g. Digoxin with a very small dose.
  - If the study is to be done using patients that are already on the drug.
  - If the drug has long have life i.e. $t_{1/2}$ of 7days or longer

TUTORIAL QUESTION

Time (min)	Concentration (μml^{-1})		
	Product A	Product B	Product C (IV Bolus)
0.5	3.4	1.23	3.43
1.0	6.0	1.94	3.22
1.5	7.9	2.20	2.45
2.0	9.3	2.64	1.43
2.5	10.3	2.86	1.32
3.0	10.9	3.43	1.20
4.0	11.6	3.22	1.05
6.0	11.4	2.45	
8.0	10.5	1.43	
12.0	8.3	1.32	
18.0	5.7	1.20	
24.0	3.8	1.05	

25

Multiple dose study

- Involves administration of the same dose of the drug at constant time intervals.
- If the time interval between administrations is less than 3 X the ½ life of the drug, each dose leads to an accumulation until a time is reached when the rate of appearance of the drug equals the rate of its elimination.
- This level is known as the *steady state level* i.e. the level at which the Cmax is no longer increasing.

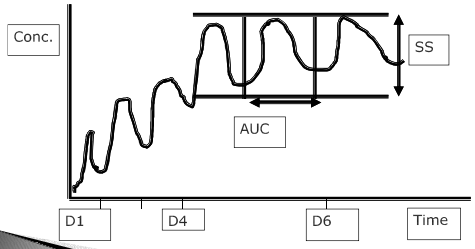
2/8/2011 26

Multiple dose study (cont.)

- Generally for all drugs, the time to achieve the steady state level depends on the ½ life and not on the dosage intervals.
- The time to achieve the steady state is 7 times (7x) the ½ life irrespective of the dosage interval, provided, of course, that there is accumulation.
- To achieve an immediate steady state level, a loading dose should be administered.

2/8/2011 27

Steady state level after multiple dose administration



2/8/2011 28

AUC in steady state level

- Once the drug is in the steady state level, e.g. on the 8th dose, blood samples can be collected within the time interval and the AUC determined, from which the bioavailability can be calculated using the equation:

2/8/2011 29

Absolute Bioavailability at SS_l

$$B_A = \frac{AUC_{ssl,oral}}{AUC_{ssl,iv}} x100\%$$

ssl = steady state level

2/8/2011 30

Relative Bioavailability at SS_I

$$B_R = \frac{AUC_{test,ssl,oral}}{AUC_{std,ssl,oral}} x100\%$$

Use of Metabolite in Bioavailability

- For drugs that are completely metabolized in the body, the metabolite level can be used for the estimation of bioavailability
- A condition has to be fulfilled: such a drug must not undergo extensive first pass metabolic effect.
- 1st pass effect must have produced some metabolite before the drug is bioavailable (i.e. reaches the systemic circulation)