PHARMACOKINETICS OF MULTIPLE DOSING

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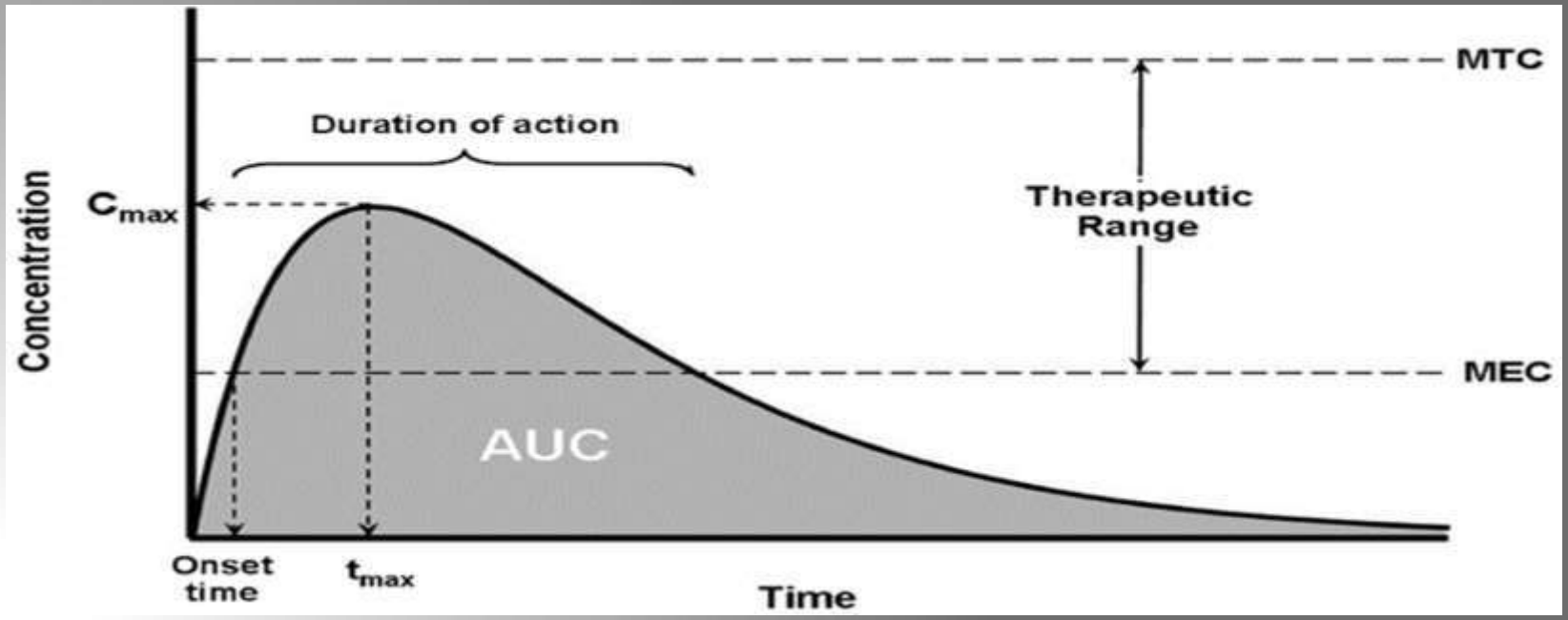
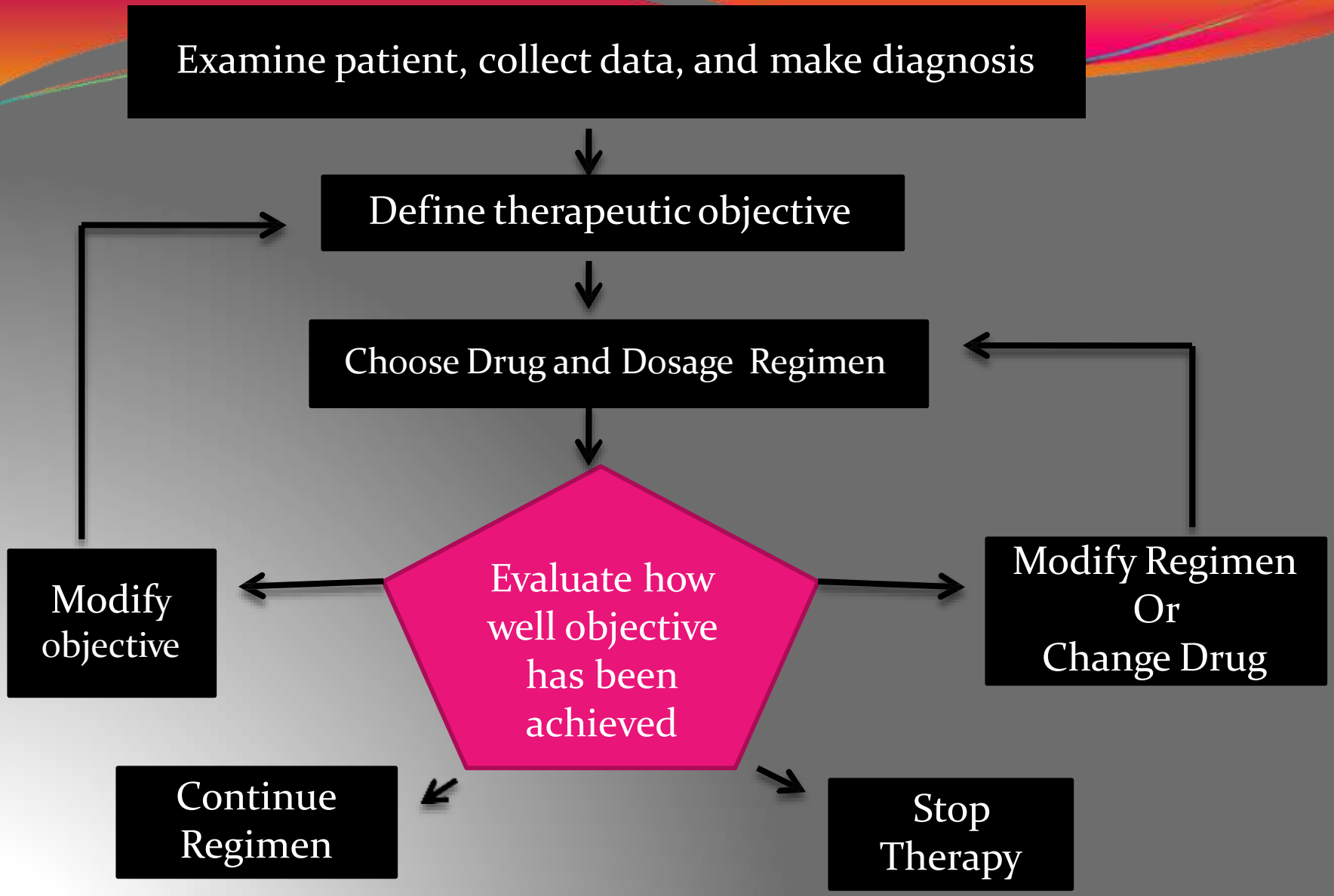
Dosage regimen

- It is defined as the manner in which a drug is taken. For certain analgesics, hypnotics, anti-emetics etc. a single dose may provide an effective treatment. But the duration of most illness is longer than the therapeutic effect produced by a single dose. In such cases drugs are required to be taken on a repetitive basis over a period of time.

Objective of dosage regimen

- The overall objective of dosage regimen design is to achieve a target drug concentration at the receptor site





Steps in the initiation and management of the drug therapy

Therapeutic Drug Monitoring

- The success of Drug therapy is highly dependent on
  - Choice of Drug and Drug Product
  - Design of the Dosage Regimen
- While the choice of Drug and Drug product is based on
  - Patient's characteristics
  - Pharmacokinetic of Drug

- Every patient have different Drug absorption, distribution, and elimination as well as different pathophysiological condition, so for the improvement in the clinical effectiveness of the drug THERAPEUTIC DRUG MONITORING are done.

- It specializes in the measurement of medication levels in blood. Its main focus is on drugs with a narrow therapeutic range, i.e. drugs that can easily be under- or overdosed.

- Therapeutic drug monitoring is important as Insufficient levels of drug in the plasma will lead to under treatment or resistance, and excessive levels can lead to toxicity and tissue damage.

Indications for TDM include:

- There is narrow therapeutic window.
- There are potential patient compliance problems.
- The drug dose cannot be optimized by clinical observation alone.
- Knowledge of the drug level influences management.

Sampling and drug analysis

- Usually, plasma or serum is used for drug assays.
- Drug assay methods should have adequate sensitivity, be specific for the drug (or metabolite) to be measured and have appropriate accuracy and precision.
- Automated immunoassay methods, High performance liquid chromatography (HPLC) and Gas liquid chromatography (GLC) (e.g. amiodarone, perhexiline) can be used.

Examples of drugs analyzed by therapeutic drug monitoring :

1. Cardio active drugs : amiodarone, digoxin, digitoxin disopyramide, lignocaine, procainamide, propranolol and quinidine
2. Antibiotics : gentamycin, amikacin and tobramycin
3. Antidepressants : lithium and tricyclic antidepressants

Function of Therapeutic Drug Monitoring

Selection of Drug

Dosage Regimen Design

Evaluation of Patient Response

To Determine need for measuring serum drug conc.

Monitoring serum drug concentration

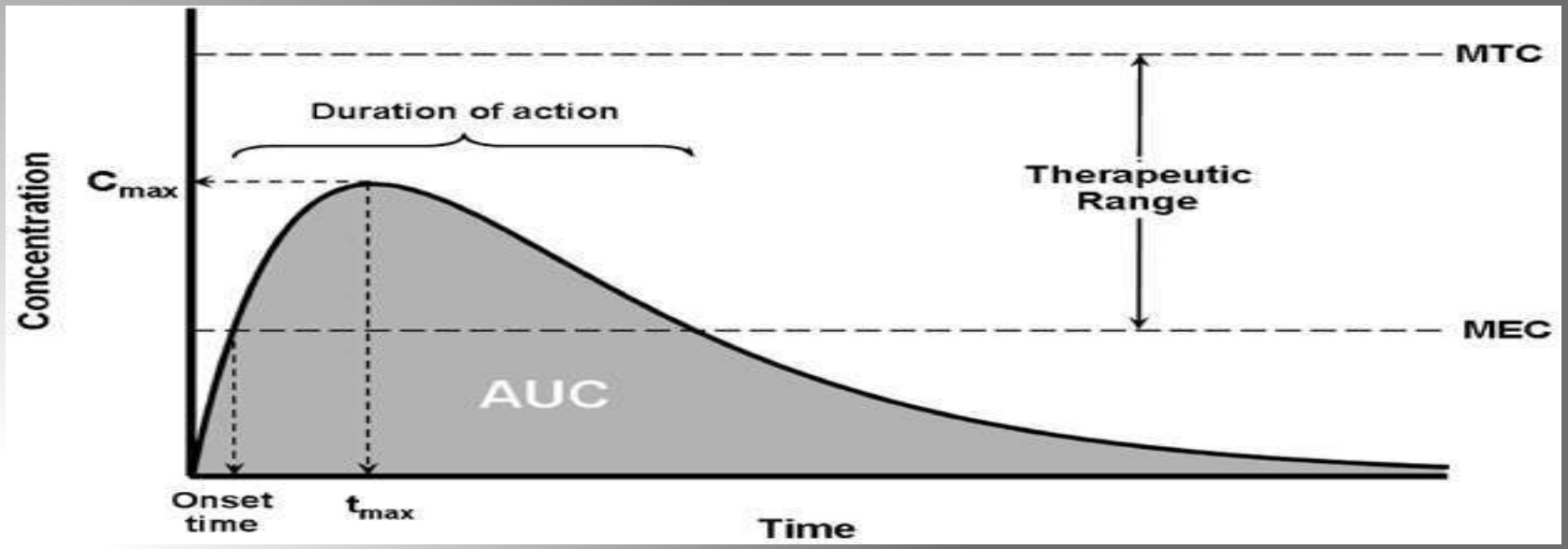
Assay of drug concentration in biological fluid

Pharmacokinetic evaluation of drug concentration

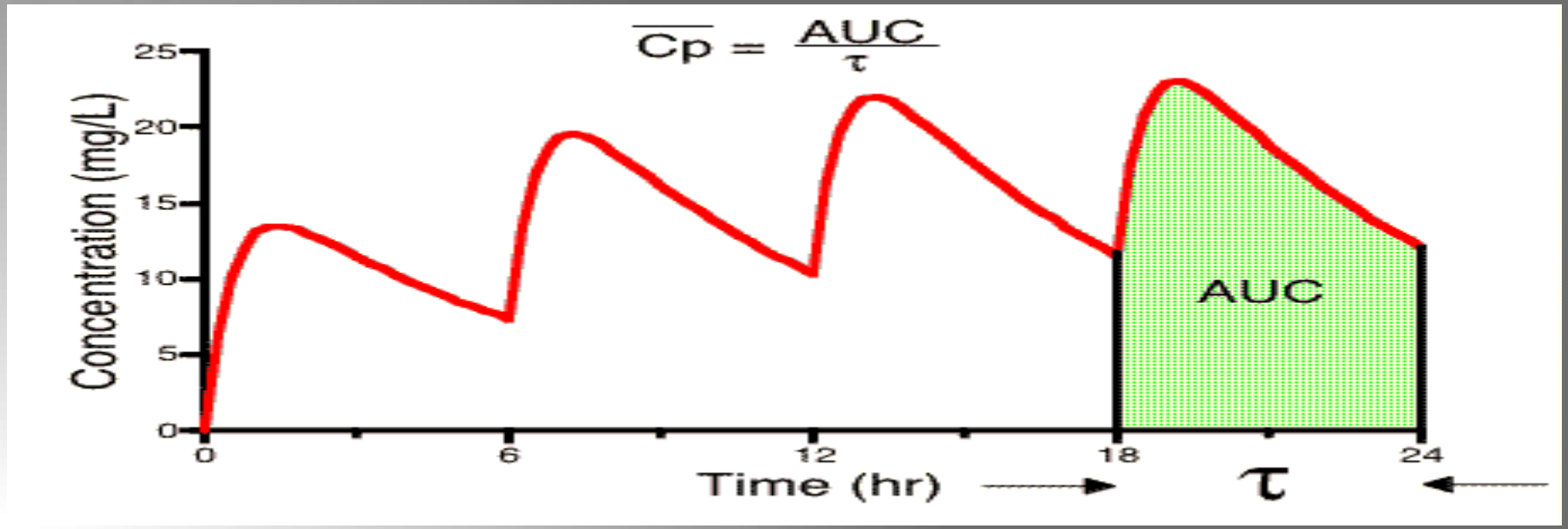
Recommend special requirement.

Multiple dosage regimen

- When the duration of treatment of disease is smaller than the therapeutic activity of drug, single dose are given e.g. Aspirin



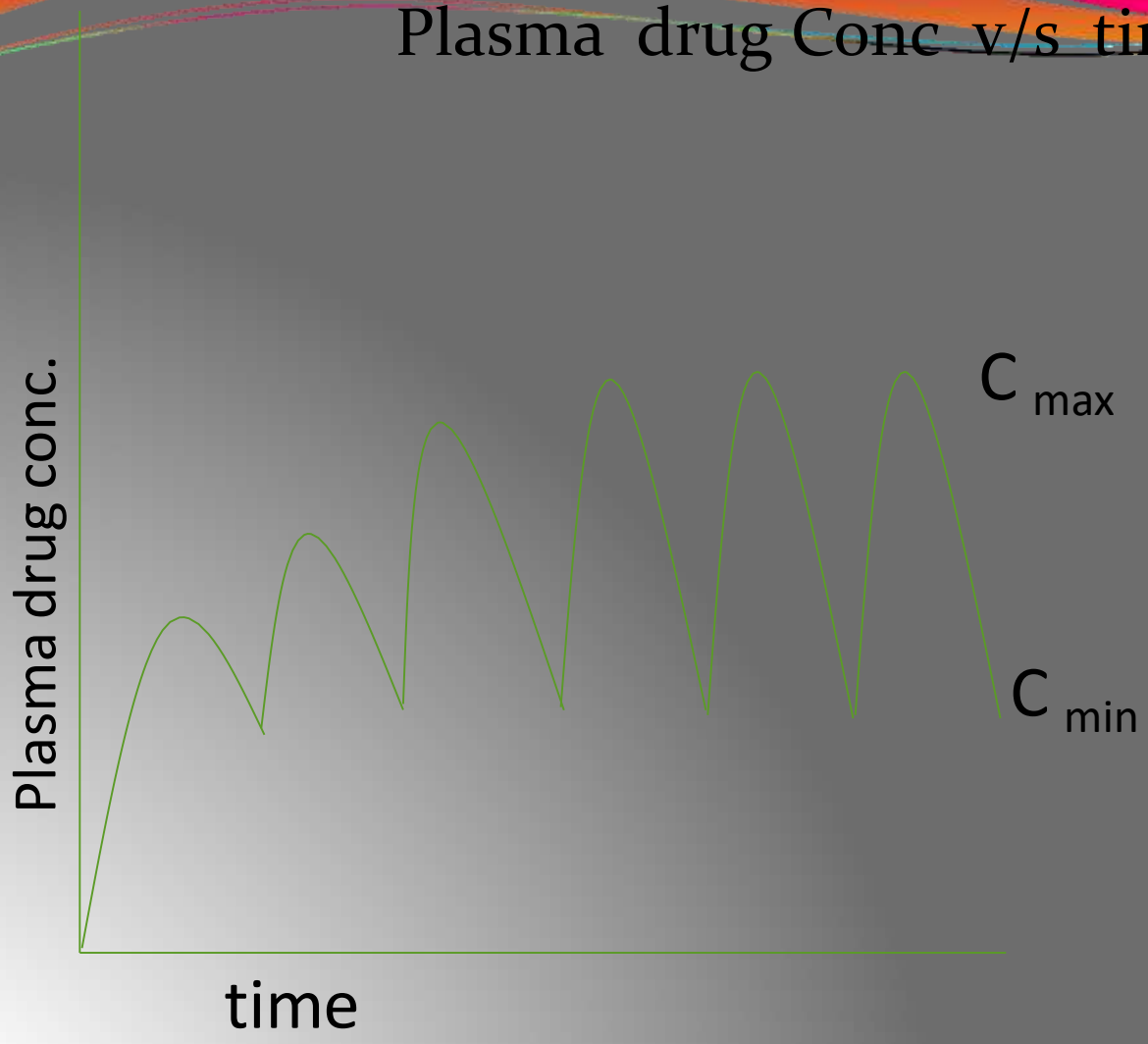
When the duration of treatment of disease is larger than the therapeutic effect of drug, Multiple dosage regimen are given e.g. antibiotics



Multiple dosing with respect to oral route

- When an oral multiple dosing regimen is followed, plasma conc. will increase, reach a maximum and begin to decline. A 2nd dose will be administered before all of the absorbed drug from 1st dose is eliminated.
- Consequently plasma conc. resulting from 2nd dose will be higher than from 1st dose. This increase in conc. with dose will continue to occur until a steady state is reach at which rate of drug entry into the body = rate of exit

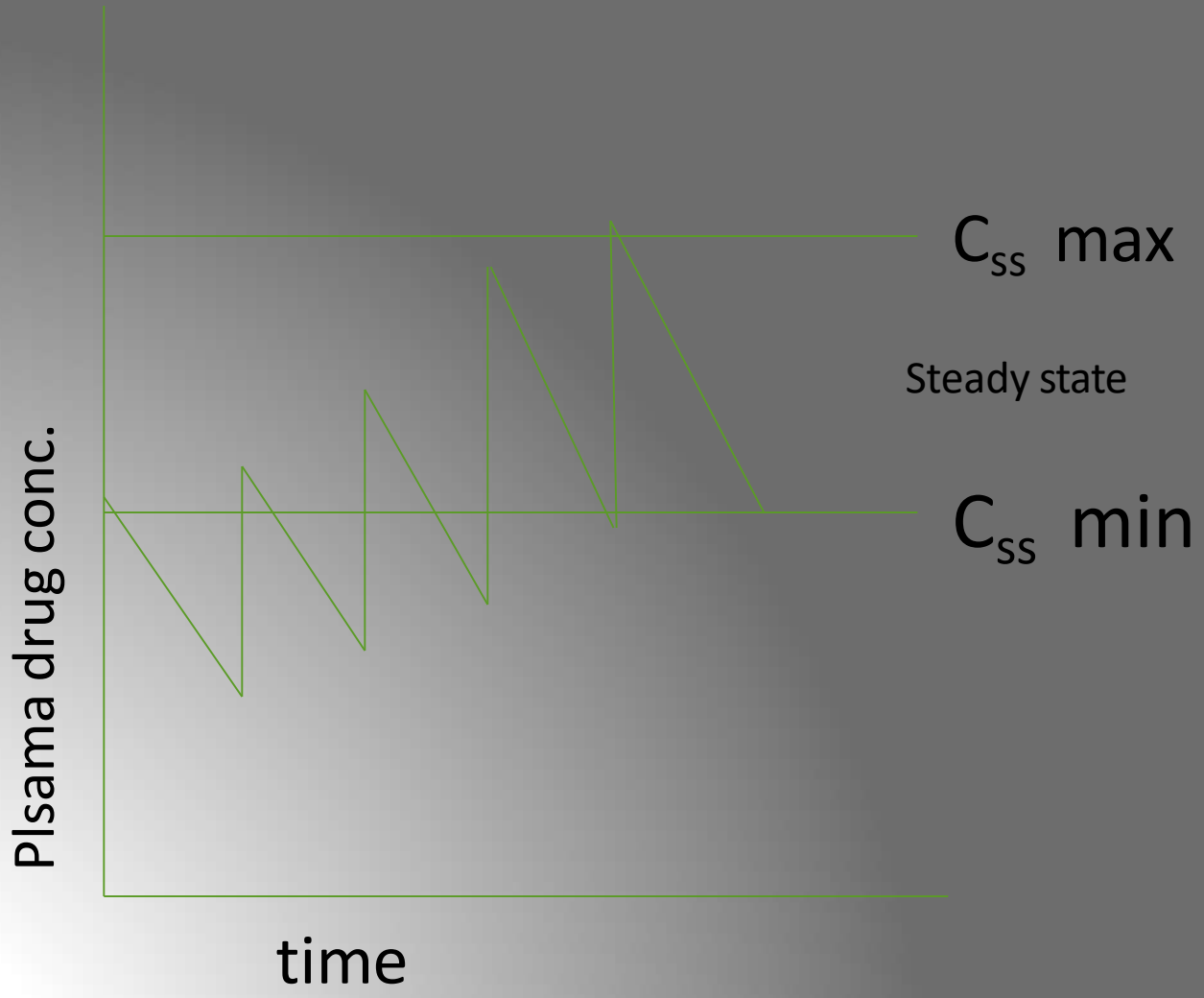
Plasma drug Conc v/s time



Multiple dosing with respect to I.V.

- On repeated drug administration, the plasma conc. will be added upon for each dose interval giving a plateau or steady state with the plasma conc. fluctuating between a minimum and maximum

Plasma drug concentration v/s time



Drug Accumulation -

When the drug is administered at a fixed dose and a fixed dosing interval, "*accumulation occur because drug from previous dose has not been remove.*"

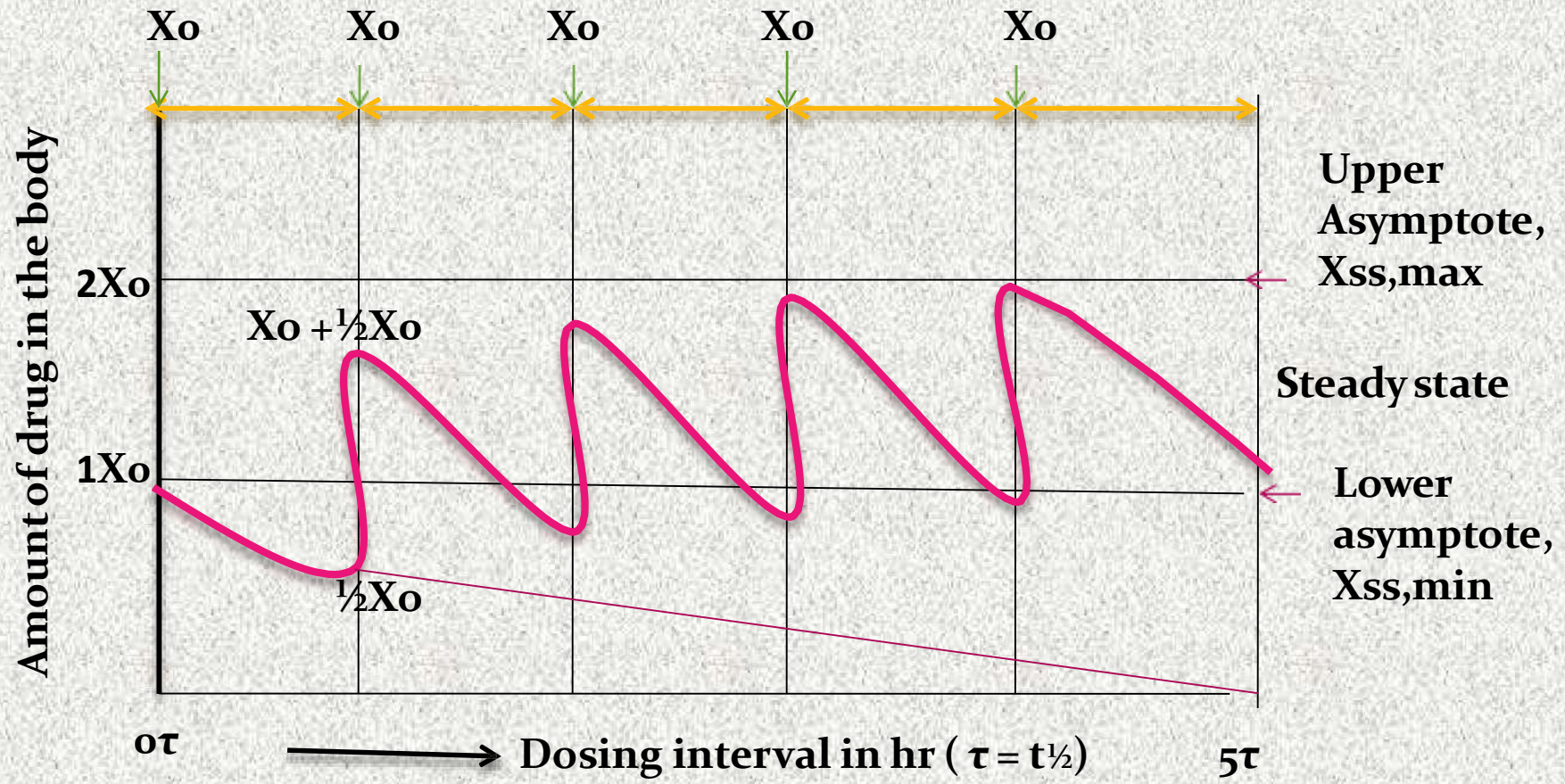
Accumulation of drug depend upon the *dosing interval* and *elimination half life* and is independent of the dose size.

$$\text{Accumulation index} = \frac{1}{1 - e^{-K_E \tau}}$$

τ= Dosing interval

K_E = Elimination half life

In drug accumulation,
Time for 90% steady state plasma conc. – 3.3 times of elimination half life.
Time for 99% steady state plasma conc. – 6.6 times of elimination half life



- e. g. of Drug Accumulation

- For a avg. adult , rate of metabolism of ethanol is 10 gm/hr
- 45 ml of whiskey contain 14 gm of ethanol.
- If drink 45 ml of whiskey every hr, will accumulate 4 gm ethanol per hr and develop coma in 48 hr.
- However, can drink 30ml whiskey (9 gm ethanol) every hr.

REPETITIVE INTRAVENOUS INJECTION

After single rapid IV injection,

$$D_B = D_o e^{-kt}$$

If the τ is the dosing interval, then amount of drug remaining in the body after several hr,

$$D_B = D_o e^{k\tau}$$

The fraction of the Dose remaining in the body

$$f = D_B/D_o = e^{-k\tau}$$

Problem of missed Dose -

Plasma drug conc. at t hr after the nth dose-

$$C_p = D_0 e^{-kt} (1 - e^{-nk\tau}) / V_D (1 - e^{-k\tau}) \ldots\ldots 1$$

Conc. contributed by missing dose is

$$C_p' = D_0 e^{-k\, t_{miss}} / V_D \ldots\ldots\ldots\ldots\ldots\ldots\ldots 2$$

So missing dose, (eq 1 – eq 2)is

$$C_p = D_0(1 - e^{-nk\tau})(e^{-kt} - e^{-k\, t_{miss}}) / V_D(1 - e^{-kt})$$

INTERMITTENT INTRAVENOUS INFUSION

- The drug may not reach steady state

Short IV infusion → Elimination period → Another short IV infusion

Conc. after one or more short IV infusion

$$C_p = D\,(1 - e^{-k\,t}) \,/\, t_{inf}\, V_D\, k$$

Where , D / t_{inf} = Rate of infusion .i.e. R

D = Size of infusion dose

t_{inf} = infusion period

V_D = volume of distribution

k = elimination rate constant

Drug conc. post IV infusion is

$$C_p = C_{stop}\, e^{-kt}$$

Where, C_{stop} = Conc. when infusion stop

t = time elapsed since infusion stopped

MULTIPLE – ORAL- DOSE REGIMEN

The plasma conc. at any time during oral multiple dose regimen,

$$Cp = \frac{F.ka.Do}{V_D(k - ka)}\left[\left\{\frac{1 - e^{-nka\tau}}{1 - e^{-ka\tau}}\right\}e^{-kat} - \left\{\frac{1 - e^{-nk\tau}}{1 - e^{-k\tau}}\right\}e^{-kt}\right]$$

Where, n= no. of doses

τ = dosing interval

F = fraction of dose absorbed

FOR MULTIPLE ORAL DOSE

$$C_{av}^{\infty} = F\ D_0 / Cl_T\ \tau$$

$$C_{max}^{\infty} = F\ D_0\ e^{-k\ tp} / V_D\ (1 - e^{-k\tau})$$

$$C_{min}^{\infty} = ka\ F\ D_0\ e^{-k\tau} / V_D\ (ka - k)(1 - e^{-k\tau})$$

Max. Conc. & min. Conc. during multiple dosing

$$C_{ss,max} = C_o / 1 - e^{-k\tau}$$

$$C_{ss,min} = C_{ss,max} . e^{-k\tau}$$

Ratio of Cmax / Cmin is known as fluctuation , Greater the ratio, greater the fluctuation.

$$\mathbf{C_{ss,av} = F X_o / Cl_T .\tau.}$$

LOADING AND MAINTENANCE DOSE

An *initial or first dose* intended to be *therapeutic* is called as priming or ***loading dose***

$$D_{o,L} = C_{ss,av} \; V_D \; / \; F$$

For 1 compartment model,

$$LD = \frac{V_D \times D_{(P)target}}{F}$$

For 2 compartment model,

$$LD = \frac{V_{D(ß)} \times D_{(P)target}}{F}$$

OBJECTIVE- to achieve desired plasma conc., C_{av}^{∞}, as quickly as possible.

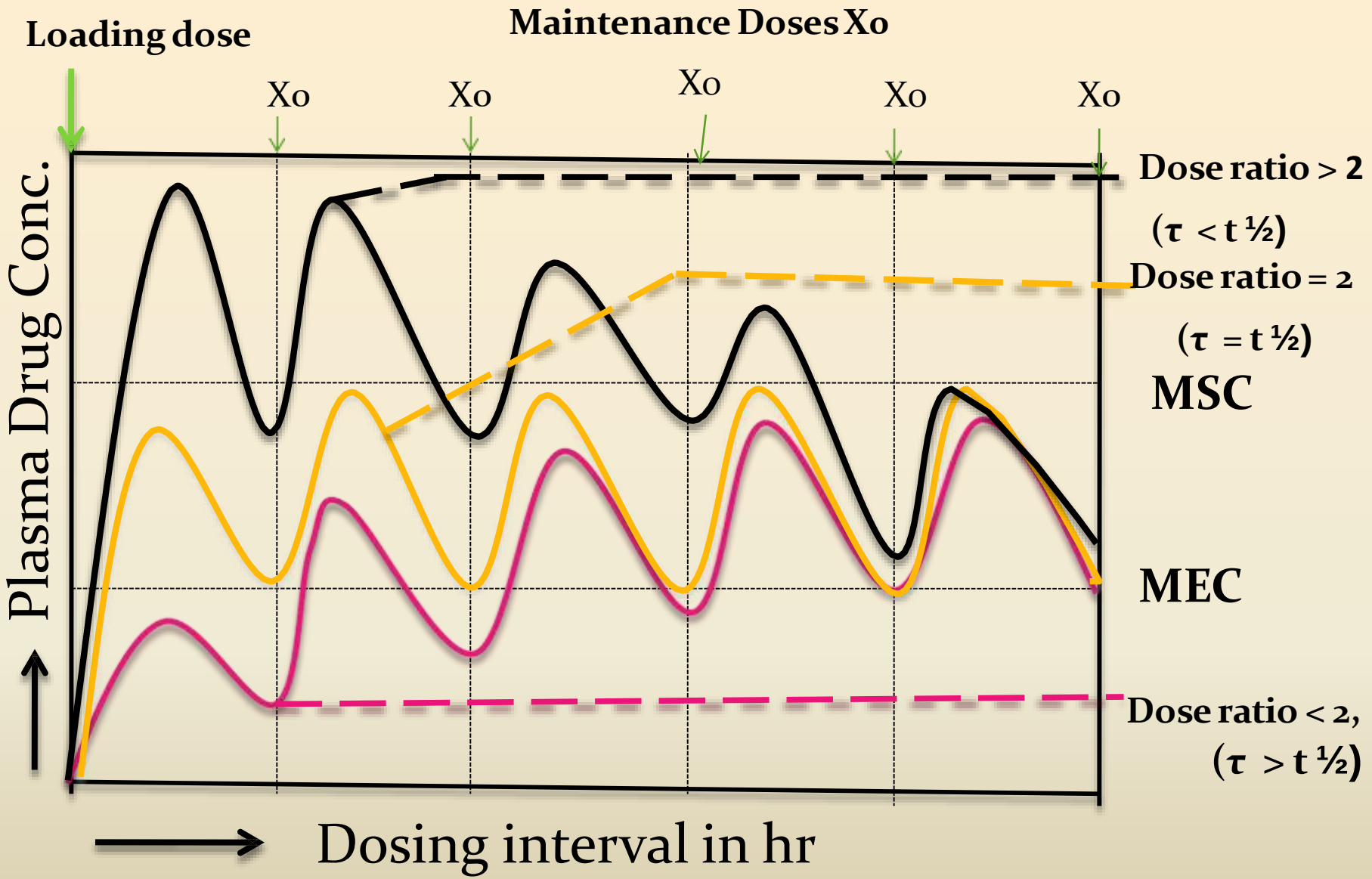
$$DI_{max} = 1.44\ t_{½} \times \log TW$$

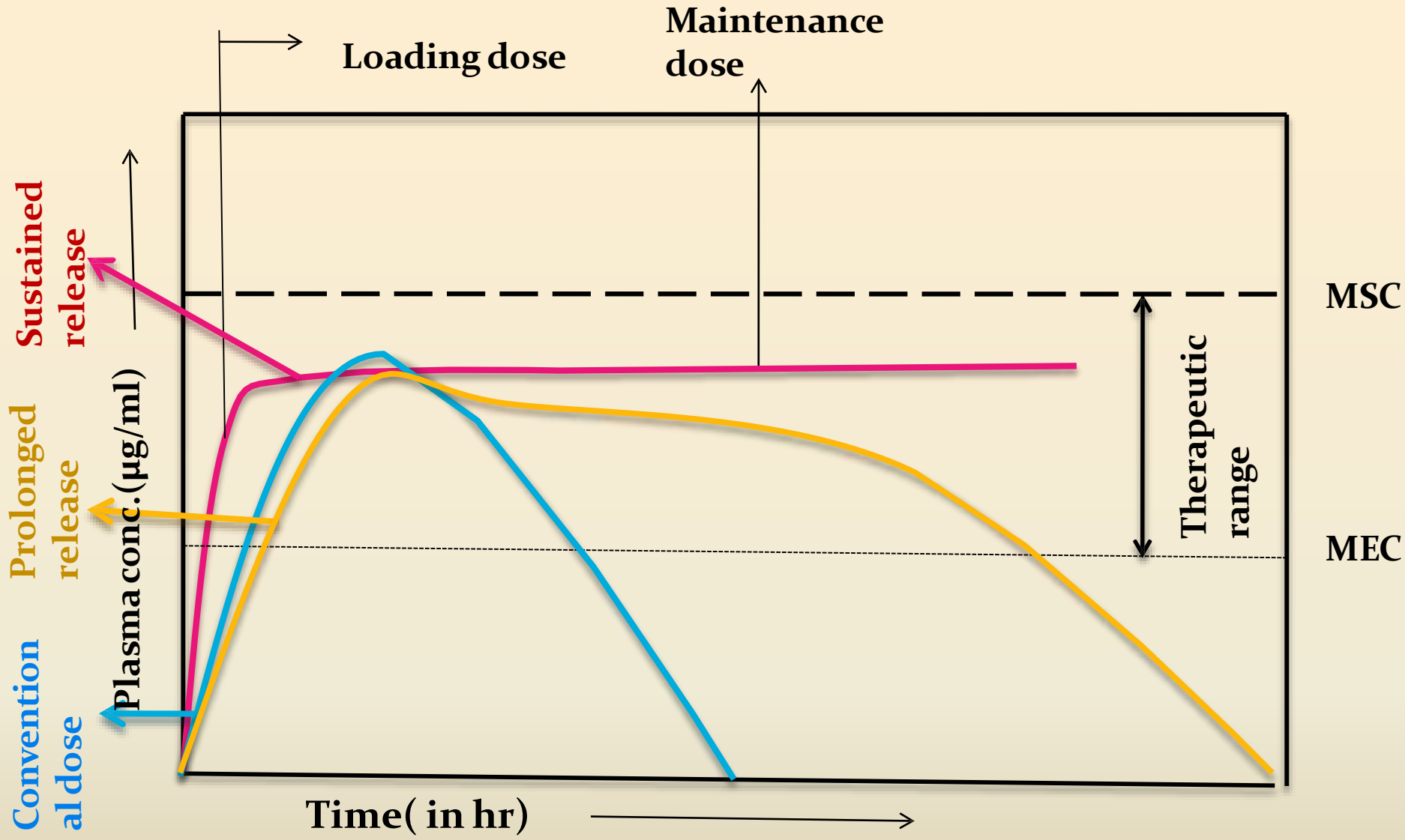
$$\text{While, } TW = \frac{MSC}{MEC}$$

$$\text{Route of Drug administration (MD /DI)} = \frac{D_{(P)}\text{target} \times Cl}{F}$$

- A **maintenance dose** is given to maintain C_{av}^{∞} and ***steady state*** so that the therapeutic effect is also maintained

- The ratio of loading dose to maintenance dose
- ***Xo, L / Xo*** , is called as ***Dose ratio***
- When, $\tau = t_{½}$, dose ratio should be equal to 2
- $\tau > t_{½}$, dose ratio should be smaller than 2
- $\tau < t_{½}$ dose ratio should be greater than 2


Loading dose
Maintenance Doses Xo
Xo
Xo
Xo
Xo
Xo
Plasma Drug Conc.
Dose ratio > 2
(τ < t ½)
Dose ratio = 2
(τ = t ½)
MSC
MEC
Dose ratio < 2,
(τ > t ½)
Dosing interval in hr



Plot showing the effect of loading dose and maintenance dose.

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THANKING YOU. . .