IN-VITRO DISSOLUTION STUDIES FOR SOLID DOSAGE FORMS, METHODS AND INTERPRETATION OF DISSOLUTION DATA

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Drug absorption from a solid dosage form after oral administration depends on the release of the drug substance from the drug product, the dissolution or solubilization of the drug under physiological conditions, and the permeability across the gastrointestinal tract.

Today, dissolution studies are the most frequently used tools in the development, characterization, and utilization process of both immediate and controlled-release formulations.

Dissolution, in the simplest sense, can be defined as the sequence by which a solid solute enters into a solution in the presence of a solvent. We can define the dissolution rate as the amount of ingredient in a solid dosage form dissolved in unit time under particular conditions.

Theories of Drug Dissolution

I. Diffusion layer model/Film Theory

II. Danckwert's model/Penetration or surface renewal Theory

III. Interfacial barrier model/Double barrier or Limited solvation theory

Dissolution testing: conventional tablets and capsules

- It measures the portion (%) of the API that (1) has been released from tablets/capsules and (2) has dissolved in the dissolution medium during controlled testing conditions within a defined period
  - The tablet thus first disintegrates
  - Then the API will be able to dissolve
  - Slow disintegration ➜ slow dissolution
  - The % API dissolved is determined with an appropriate validated method: UV/VIS, HPLC, etc

- Dissolution testing is also applicable to suspensions and suppositories

Solid oral dosage forms

Immediate release typically means that 75% of the API is dissolved within 45 minutes

- Rapidly dissolving: ≥ 85% in ≤ 30 minutes
- Very rapidly dissolving: ≥ 85% in ≤ 15 minutes

Dissolution is principally useful as a QC test. It **can be** predictive of in vivo behaviour, but this must be demonstrated by an in-vivo in-vitro correlation study (IVIVC).

- The FDA guidance on dissolution testing for immediate release solid oral dosage forms1 includes the use of the Biopharmaceutics Classification System (BCS)
- The Biopharmaceutics Classification System (BCS) combines physicochemical properties of compounds and physiological factors to predict the fraction dose absorbed from the gastrointestinal transit.

"BCS is a scientific framework for the classification of drug substances based on their aqueous solubility and intestinal permeability."

BCS Classes:

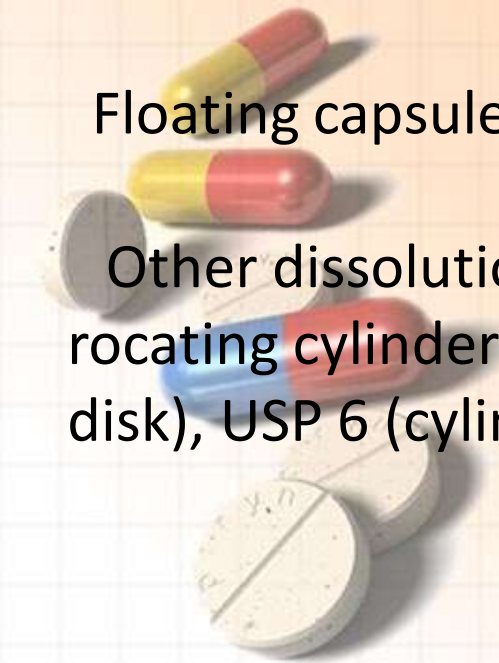
- According to the BCS, drug substances are classified as follows:
  - Class 1: High Solubility – High Permeability
  - Class 2: Low Solubility – High Permeability
  - Class 3: High Solubility – Low Permeability
  - Class 4: Low Solubility – Low Permeability

DISSOLUTION AND DRUG RELEASE TESTING
METHOD DEVELOPMENT FOR IMMEDIATE RELEASE DOSAGE FORMS

For solid dosage forms, industry standard dissolution test-ing methodologies are the United States Pharmacopoeia (USP) Apparatus 1 (basket) 100 rpm and the USP Apparatus 2 (paddle) 50 rpm.

Lower stirring speed is chosen in accordance with the test data

Immediate-release, modified-release and extended release tab-lets are usually tested in classical dissolution baths with USP 2 pad-dles.

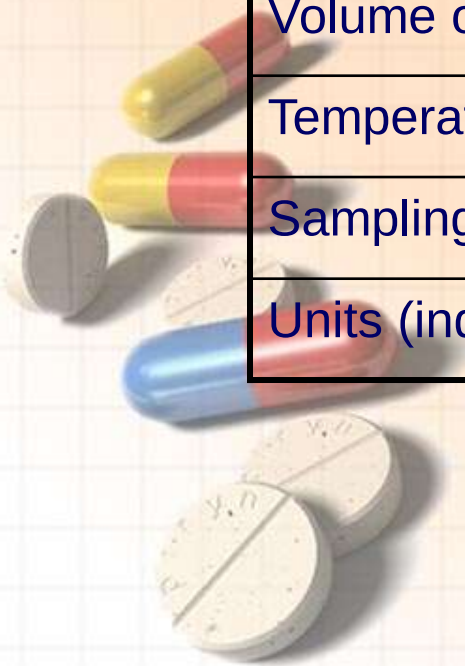


Floating capsules and tab-lets generally use USP 1 baskets.

Other dissolution techniques and equipment include USP 3 (recip-rocating cylinders), USP 4 (flow-through-cell), USP 5 (paddle-over-disk), USP 6 (cylinder) and USP 7 (reciprocating holders).[5]

Comparative dissolution testing
Dissolution conditions (study design)

Apparatus(choice)	• Paddle, 50 (75) rpm or Basket, 100 rpm
Dissolution media All three media for full comparison	1. Buffer pH 6.8 or simulated intestinal fluid without enzymes 2. Buffer pH 4.5 3. 0.1 M HCl or buffer pH 1.2 or simulated gastric fluid without enzymes
Volume of media	900 ml or less
Temperature	37°C ± 0.5°C
Sampling points	10, 15, 20, 30, 45, (60, 120) min. (typical)
Units (individual)	12 for "official" studies

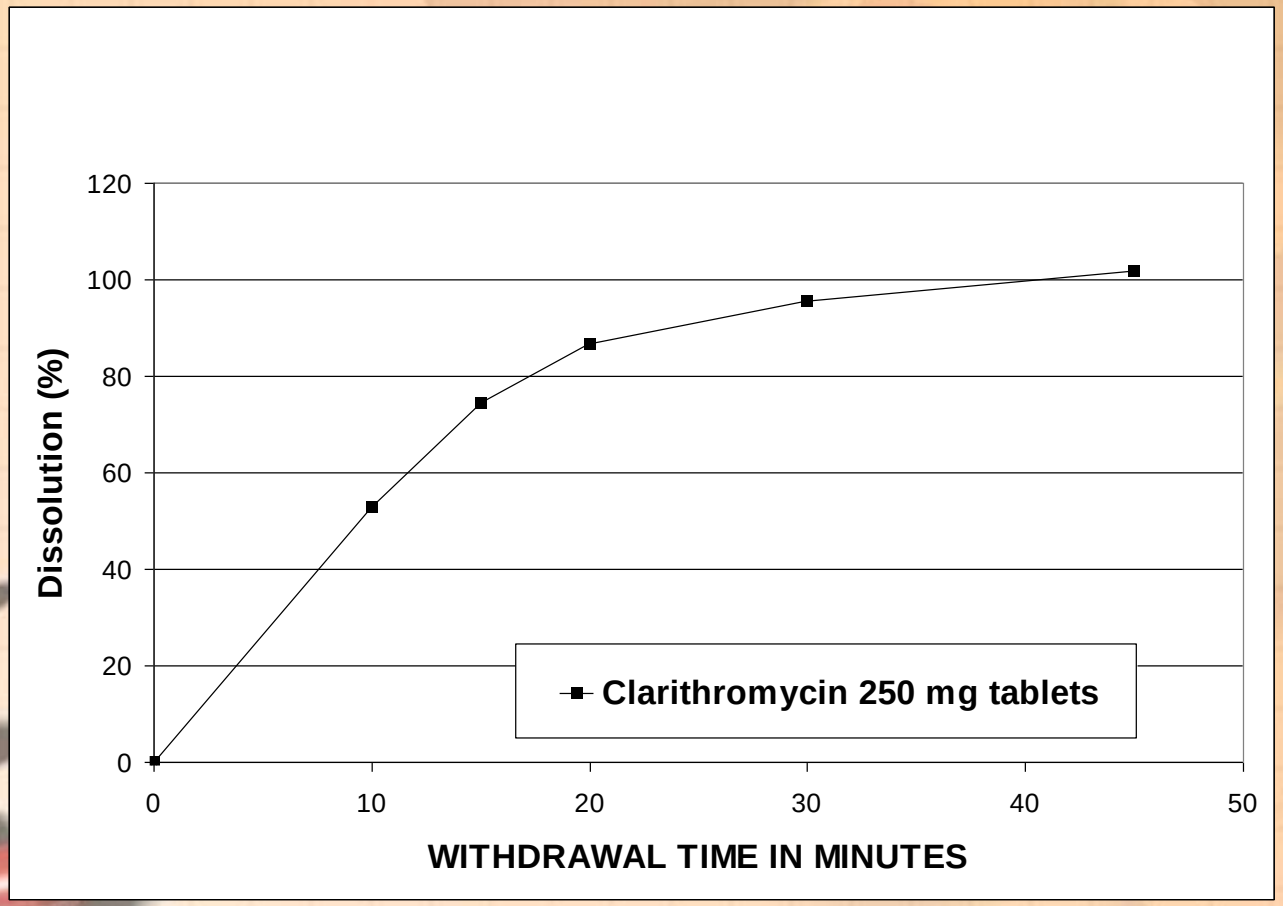


Amodiaquine HCl Tablets

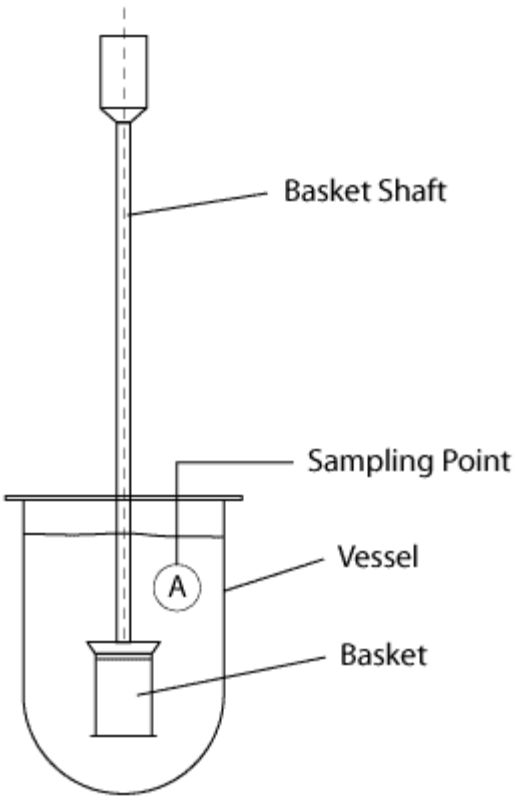
Medium: water; 900 mL.

Apparatus 2: 50 rpm.

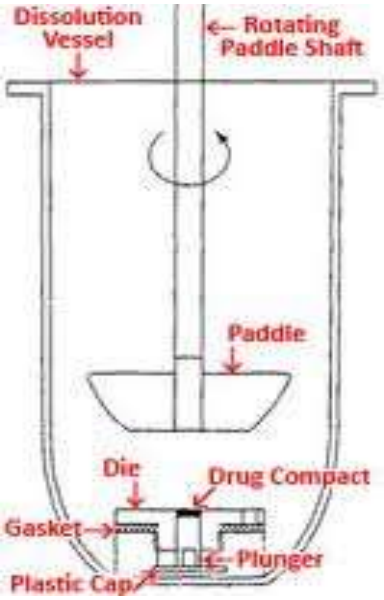
NLT 75% (Q) in 30 minutes


120
100
80
60
40
20
0
Dissolution (%)
0
10
20
30
40
50
WITHDRAWAL TIME IN MINUTES
Clarithromycin 250 mg tablets

APPARATUS 1:BASKET APPARATUS



APPARATUS 2:PADDLE APPARATUS

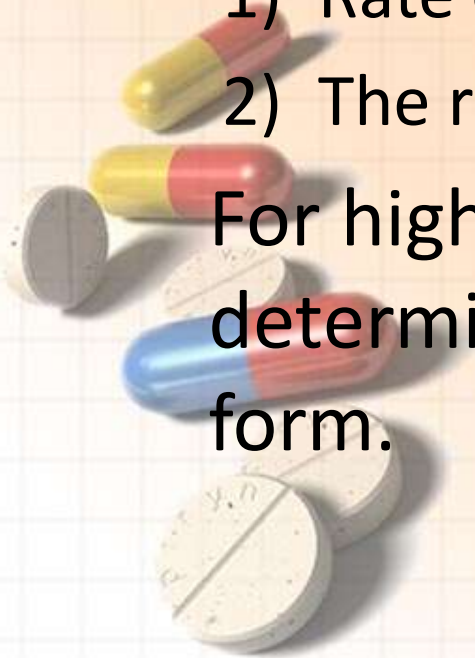


Disintegration (DT) Testing

- For immediate release tablets and capsules, dissolution rate is determined by:

  1) Rate of release of the API from the matrix, and
  2) The rate at which the API dissolves in the medium.

  For highly soluble API's, the rate is largely determined by the disintegration of the dosage form.



BIOAVAILABILITY

STUDIES AND METHODS

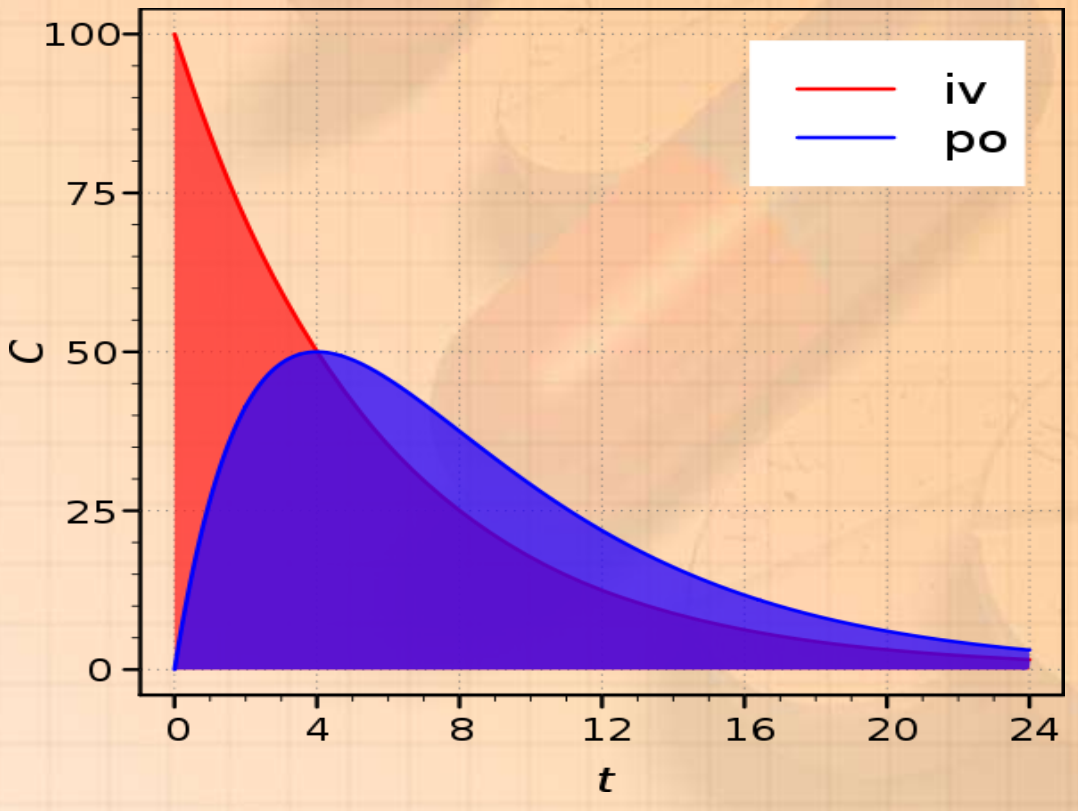
(what we get from what we have taken in)

Bioavailability is a pharmacokinetic term that describes the rate and extent to which the active drug ingredient is absorbed from a drug product and becomes available at the site of drug action

Bioavailability is concerned with how quickly and how much of a drug appears in the blood after a specific dose is administered.

The bioavailability of a drug product often determines the therapeutic efficacy of that product since it affects the onset, intensity and duration of therapeutic response of the drug.

Absolute bioavailability compares the bioavailability of the active drug in systemic circulation following non-intravenous administration (i.e., after oral, rectal, transdermal, subcutaneous, or sublingual administration), with the bioavailability of the same drug following intravenous administration

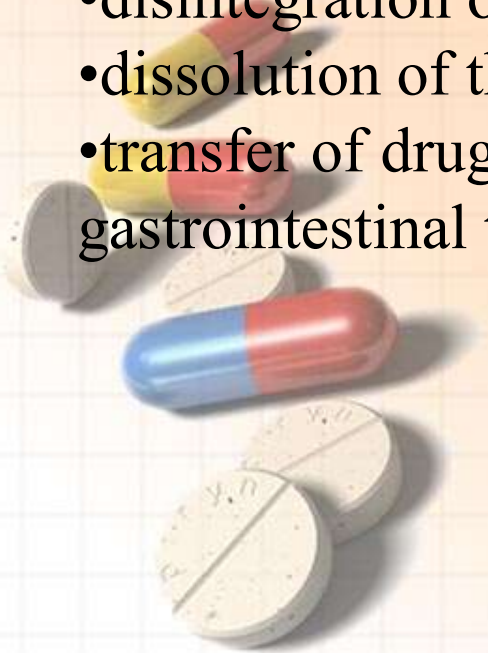


Absolute bioavailability is a ratio of areas under the curves. IV, intravenous; PO, oral route.

Relative bioavailability measures the bioavailability (estimated as the AUC) of a formulation (*A*) of a certain drug when compared with another formulation (*B*) of the same drug, usually an established standard, or through administration via a different route.

The systemic absorption of an orally administered drug in a solid dosage form is comprised of three distinct steps:

- disintegration of the drug product
- dissolution of the drug in the fluids at the absorption site
- transfer of drug molecule across the membrane lining the gastrointestinal tract into the systemic circulation.



FACTORS AFFECTING BIOAVAILABILITY

Bioavailability Factors related to the dosage form

Physicochemical properties of the drug	**Formulation and manufacturing variables**
Particle size	Amount of disintegrant
Crystalline structure	Amount of lubricant
Degree of hydration of crystal	Special coatings
Salt or ester form	Nature of diluents
	Compression force

Bioavailability Factors related to the dosage form

Physiologic factors	Interactions with other substances
Variations in absorption power along GI tract Variations in pH of GI fluids Gastric emptying rate Intestinal motility Perfusion of GI tract Presystemic and first-pass metabolism Age, sex, weight Disease states	Food Fluid volume Other drugs

Fastest availability	Solutions
	Suspensions
	Capsules
	Tablets
	Coated tablets
	Controlled-release formulations
Slowest availability	

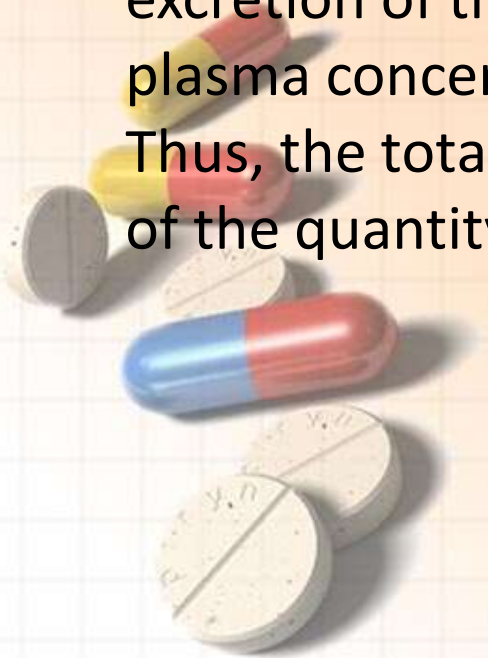
METHODS OF ASSESSING BIOAVAILABILITY

Blood level studies are the most common type of human bioavailability studies, and are based on the assumption that there is a direct relationship between the concentration of drug in blood or plasma and the concentration of drug at the site of action.

By monitoring the concentration in the blood, it is thus possible to obtain an indirect measure of drug response

An alternative bioavailability study measures the cumulative amount of unchanged drug excreted in the urine. These studies involve collection of urine samples and the determination of the total quantity of drug excreted in the urine as a function of time. These studies are based on the premise that urinary excretion of the unchanged drug is directly proportional to the plasma concentration of total drug.

Thus, the total quantity of drug excreted in the urine is a reflection of the quantity of drug absorbed from the gastrointestinal tract.



Bioavailability (the rate and extent of drug absorption) is generally assessed by the determination of these three parameters.

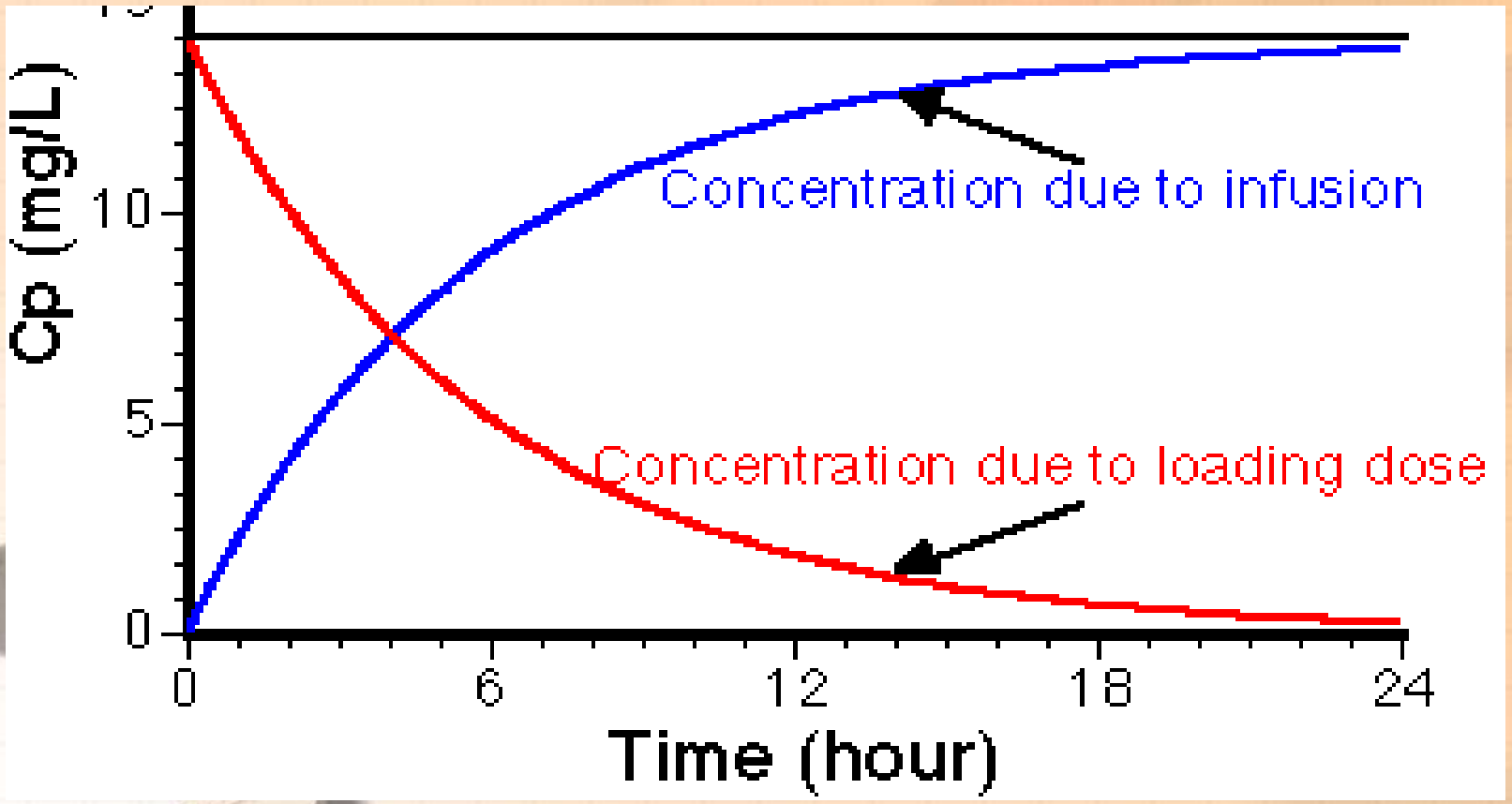
1. **AUC , The area under the plasma concentration-time curve, The AUC is proportional to the** total amount of drug reaching the systemic circulation, and thus characterizes the extent of absorption.

2. Cmax , The maximum drug concentration. The maximum concentration of drug in the plasma is a function of both the rate and extent of absorption. **Cmax will increase with an increase in** the dose, as well as with an increase in the absorption rate.

3. Tmax , The time at which the Cmax occurs. The Tmax reflects the rate of drug absorption, and decreases as the absorption rate increases.

Single dose vs. multiple dose

Time to reach steady state

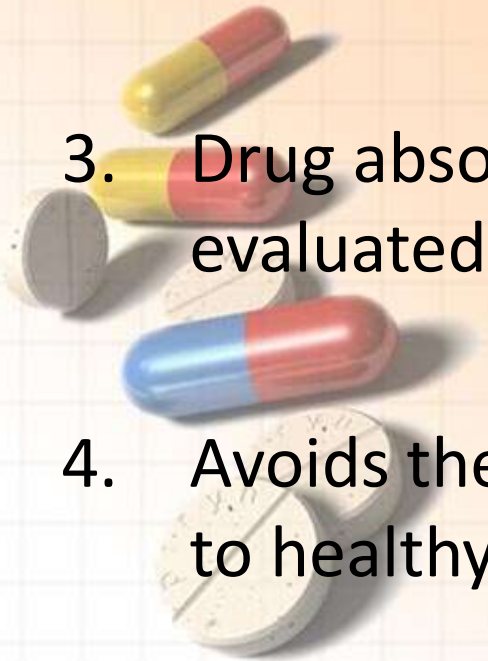


- Ideally, the bioavailability study should be carried out in patients for whom the drug is intended to be used.

Advantages :

1. Patient is benefited from the study.

2. Reflects better therapeutic efficacy of drug.



3. Drug absorption pattern in disease state can be evaluated.

4. Avoids the ethical quandary of administering drug to healthy subjects.

- There are some drawbacks of using patients as volunteers.
- Stringent conditions such as fasting state required is difficult to be followed by the patients.
- Studies are therefore performed in young (20-40 yrs.), healthy males adult volunteers.

Thank you