Bioavailability

Introduced by:

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Outlines

- Introduction
- Factors affecting bioavailability
- Assessment of bioavailability

Introduction

- Bioavailability studies are drug product performance studies used to define the effect of changes in the physicochemical properties of the drug substance, the formulation of the drug, and the manufacture process of the drug product (dosage form).
- Drug product performance studies are used in the development of new and generic drug products.

- Bioavailability is one aspect of drug product quality that links the *in vivo* performance of a new drug product to the original formulation that was used in clinical safety and efficacy studies.

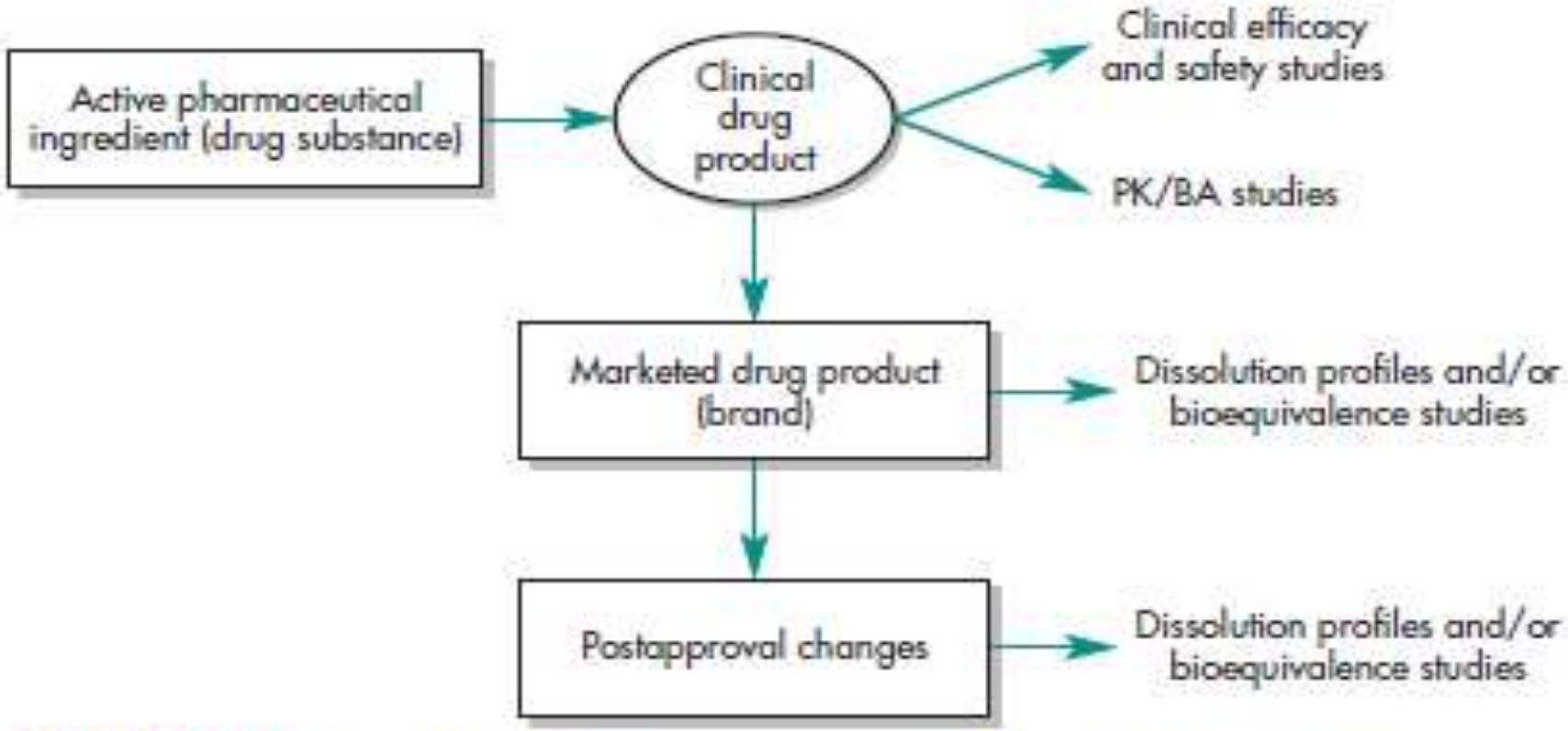


FIGURE 16-1 Drug product performance and new drug product development for NDAs. Drug product performance may be determined *in vivo* by bioequivalence studies or *in vitro* by comparative drug dissolution studies. BA = bioavailability.

Factors affecting bioavailability

- Physicochemical factors
- Dosage form factors

Physicochemical factors

1) Dissolution and solubility, any factor influencing these properties can affect the bioavailability.

Table 20.1 Physicochemical and physiological factors affecting drug dissolution in the gastrointestinal tract (adapted from Dressman et al 1998)

Factor	Physicochemical parameter	Physiological parameter
Effective surface area of drug	Particle size, wettability	Surfactants in gastric juice and bile. pH, buffer capacity, bile, food components
Solubility in diffusion layer	Hydrophilicity, crystal structure	
Amount of drug already dissolved	Solubilization	Permeability, transit
Diffusivity of drug	Molecular size	Viscosity of luminal contents
Boundary layer thickness		Motility patterns and flow rate
Volume of solvent available		Gastrointestinal secretions, co-administered fluids

Particle size reduction, micronization or nano-sizing. What are the drawbacks of this factor??

Aggregation, increase in degreadation

Table 20.2 Examples of drugs where a reduction in particle size has led to improvements in bioavailability

Drug	Therapeutic class
Digoxin	Cardiac glycoside
Nitrofurantoin	Antifungal
Medroxyprogesterone	Hormone acetate
Danazol	Steroid
Tolbutamide	Antidiabetic
Aspirin	Analgesic
Sulfadiazine	Antibacterial
Naproxen	Non-steroidal anti-inflammatory
Ibuprofen	Non-steroidal anti-inflammatory
Phenacetin	Analgesic
Griseofulvin	Antifungal
Fenofibrate	Lipid regulating agent
Megestrol acetate	Apetite loss
Aprepitant	Anti-emetic
Rapamycin	Immunosuppressant
Lapinovir/ritonavir	HIV protease inhibitors

- Ketoconazole (w.b) is particularly sensitive to gastric pH. Dosing ketoconazole 2 hr after the administration of the H_2 blocker (cimetidine), results in a significantly reduced rate and extent of absorption.
- Salt form effect on solubility, dissolution and then bioavailability (like naproxen sodium, tolbutamide sodium, barbiturate sod. salts.
- The presence o the basic excipients in the formulation of acidic drugs ensures that a relatively basic diffusion layer is formed around each dissolving particle.

- ✓ Polymorph B (metastable form) of chloramphenicol palmitate with good BA.
- ✓ Amorphous form of the antibiotic novobiocin with good BA.
- ✓ Ampicillin trihydrate and anhyraous form??
- ✓ Complexation of drugs may **increase** or **decrease** BA?? (with complexing agent, excipient, food, or mucin). Ex.

Tetracyclines + Di Ca phosphate

Amphetamine + Sod. CMC

Phenobarbital + PEG 4000

- ✓ Effect of cyclodextrins (alpha, beta and gamma) on miconazole, piroxicam, itraconazole, naproxen …etc.(increase BA.)
- ✓ Adsorbent effect ? Ex. Promazine-charcoal, talc -vit. B12.
- ✓ Enteric coating for tablets or particles.??

2) Factors affecting drug absorption, like pKa, lipophilicity, molecular size and hydrogen bonding.

- ✓ Weak acids and bases??

Table 20.3 Prodrugs with improved lipid solubility and oral absorption

Prodrug	Active drug	Ester
Pivampicillin	Ampicillin	Pivaloyloxymethyl
Bacampicillin	Ampicillin	Carbonate
Indanylcarbenicillin	Carbenicillin	Indanyl
Cefuroxime axetil	Cefuroxime	Acetylethyl
Enalapril	Enalaprilat	Ester of 1-carboxylic acid
Ibuterol	Terbutaline	Dibutyl
Valaciclovir	Aciclovir	L-valyl (amino acid)
Fosamprenavir	Amprenavir	Phosphate

- **What is the meaning of pH-partition hypothesis? Applications and limitations??**

Dosage form factors

- Influence of the type of dosage form, method of preparation or manufacture on BA.

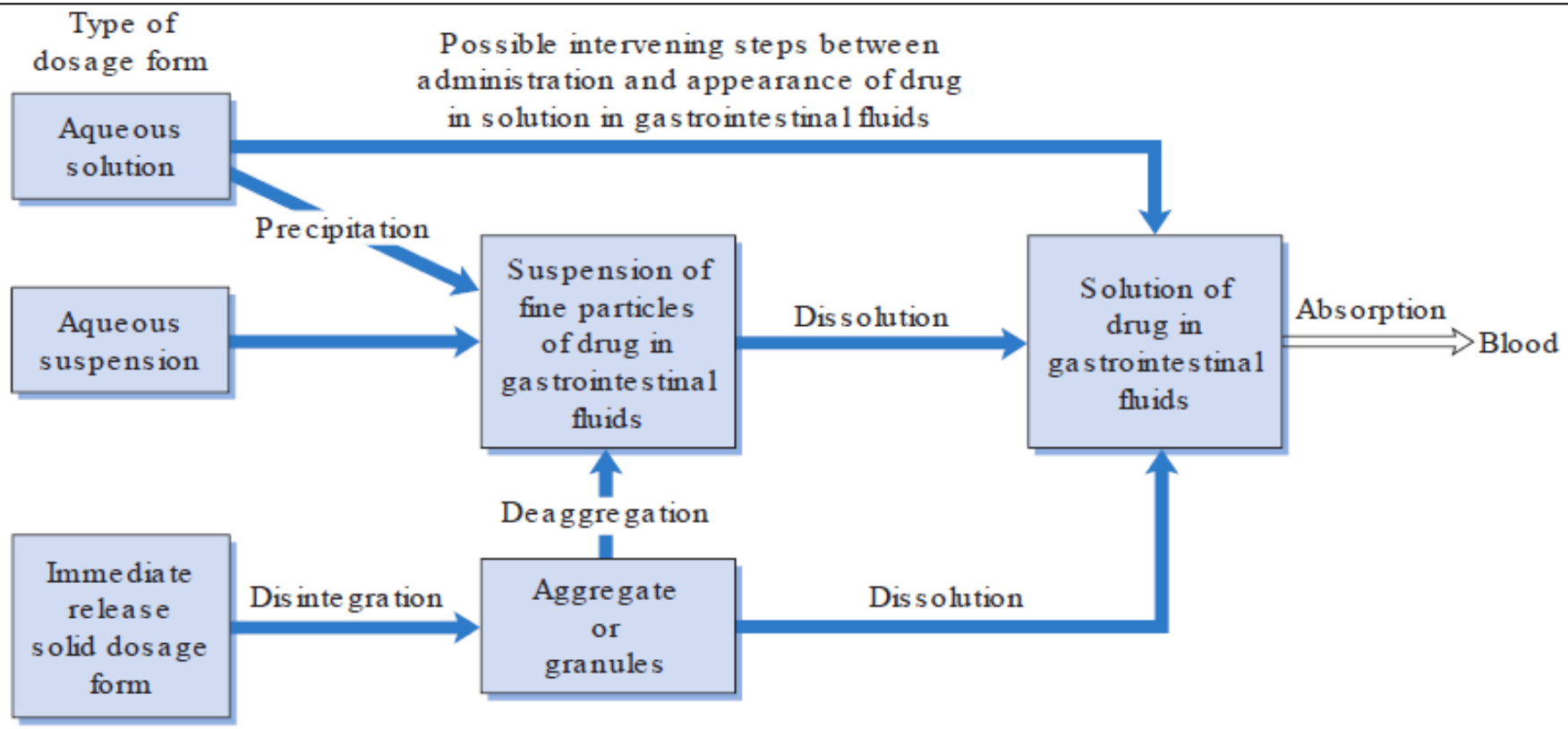


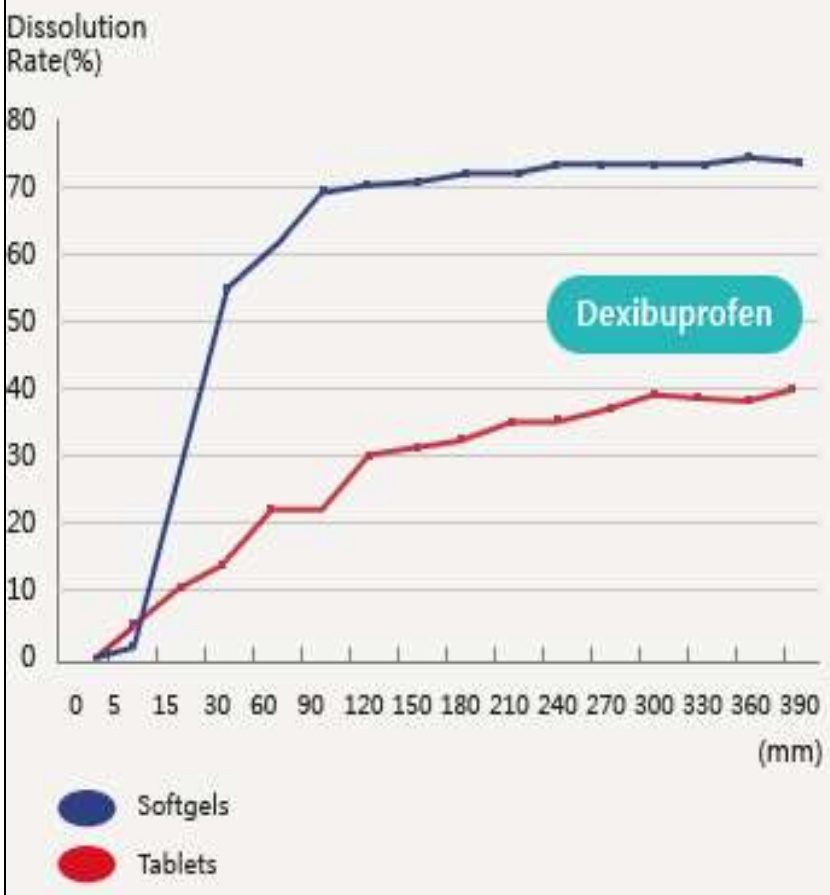
Fig. 20.2 • Schematic outline of the infuence of the dosage form on the appearance of drug in solution in the gastrointestinal tract.

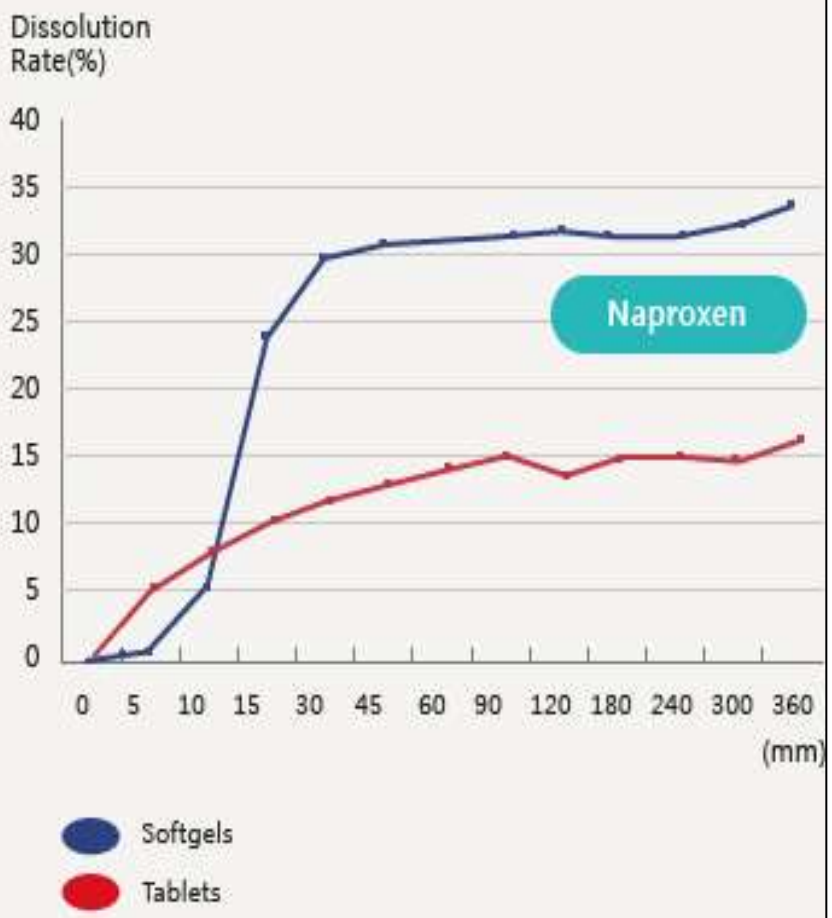
- ✓ Dilution of an aq. Solution of a poorly water-soluble drug whose aq. solubility had been increased by formulation techniques such as cosolvency, complex formation or solubilization can result in precipitation of the drug in the gastric fluids.
- ✓ Exposure of an aqueous solution of a salt of a weak acidic compound to gastric pH can also result in precipitation of the free acid form of the drug.
- ✓

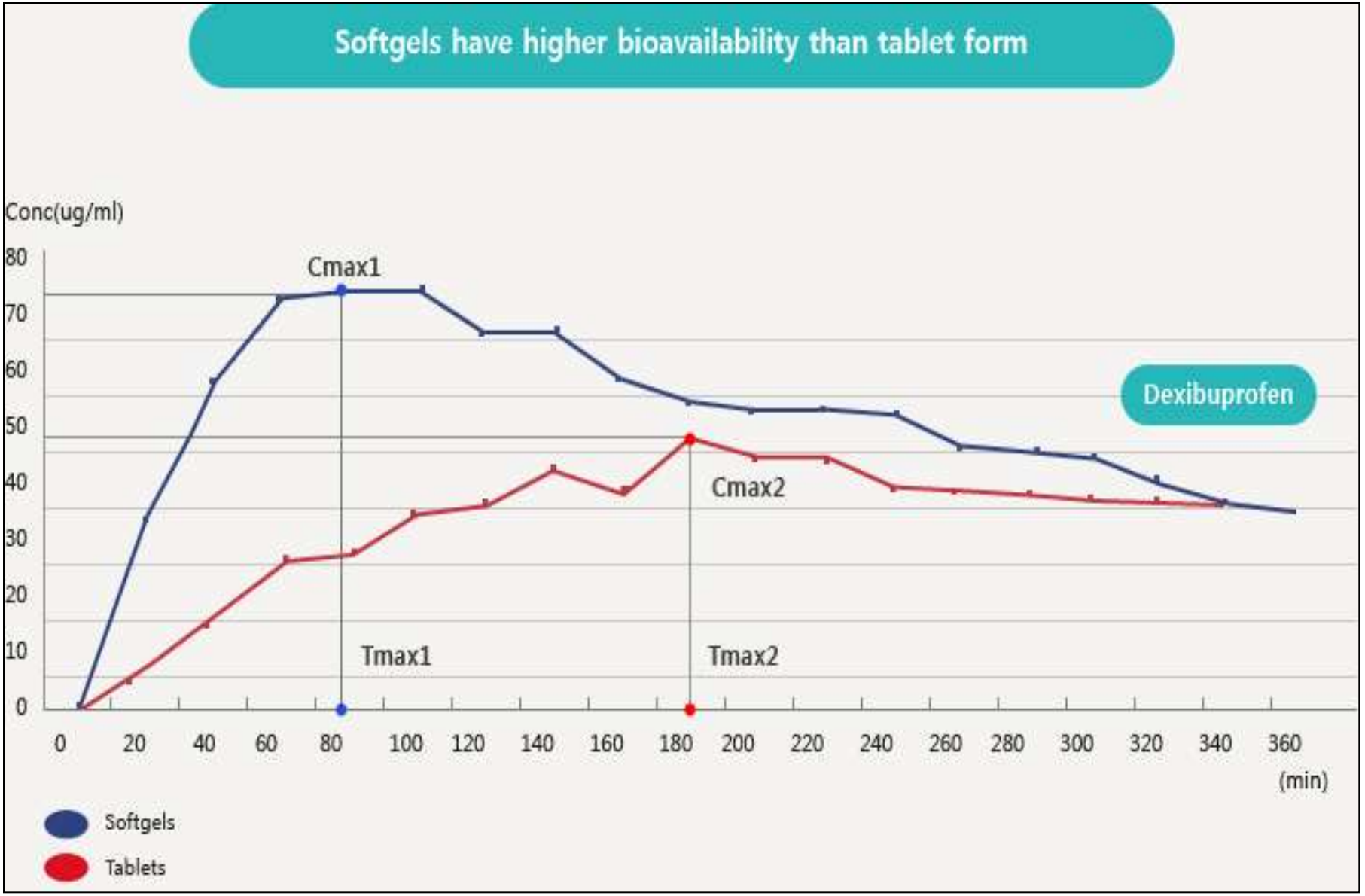
- ✓ Factors related to the aq. Solutions like complexation, stability, solubilization and viscosity.
- ✓ Factors related to the aq. Suspensions like p.s., eff. S.A., the crystal form of drug, complexation, SAA and viscosity.

- For liquid-filled capsules (as in softgels)
- ✓ With rapid absorption and good BA.??
- ✓ No ppt. possibility.
- ✓ Involve emulsification on micro- or nano-level.
- ✓ As for digoxin, cyclosporine and ibuprofen (Advil®).
- ✓ Factors affecting BA: solubility of drug in the vehicle, p.s. (if suspended), the vehicle nature, presence of SAA, viscosity and complexation.

2-time faster dissolution rate compared to tablet form

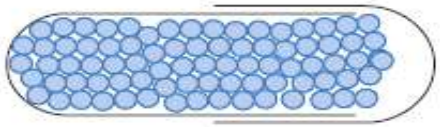




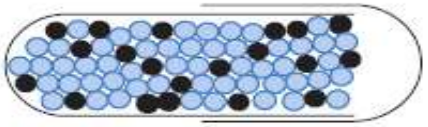

Softgels have higher bioavailability than tablet form
Conc(ug/ml)
80
70
60
50
40
30
20
10
0
Cmax1
Cmax2
Tmax1
Tmax2
Dexibuprofen
0
20
40
60
80
100
120
140
160
180
200
220
240
260
280
300
320
340
360
(min)
Softgels
Tablets

- For powder-filled capsule.
- ✓ Similar to tablets.
- ✓ Dissolution rate by inclusion of hydrophilic excipients.
- ✓ As formulation factors affecting BA, are: S.A. and p.s., chemical nature, crystal form, stability, amount and type of additives, compatibility,and shell properties.

- For tablets (coated and uncoated).
- ✓ Compaction can decrease the effective S.A.
- ✓ Disintegration, dissolution, then absorption.
- ✓ BA is effected by: S.A., wettability, crystal form, chemical stability, excipients type and amount, compatibility, granules or pellets properties, compaction pressure, storage condition, and coating layer type.



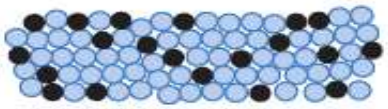
Hard gelatin capsule containing only hydrophobic drug particles



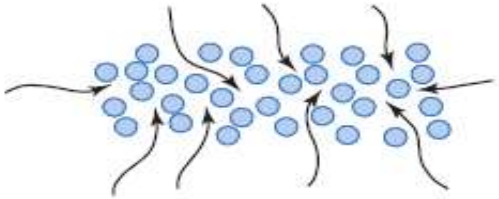
Hard gelatin capsule containing hydrophobic drug particles (○) and hydrophilic diluent particles (●)

In gastrointestinal fluids, hard gelatin capsule shell dissolves, thereby exposing contents to fluids

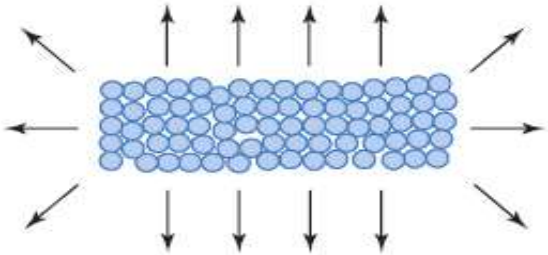
Contents remain as a capsule-shaped plug. Hydrophobic nature of contents impedes penetration of gastrointestinal fluids



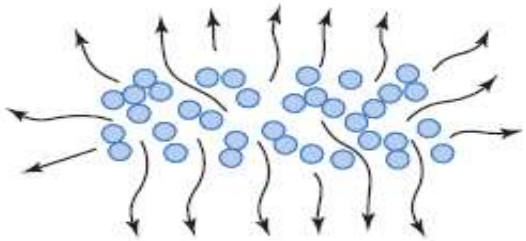
Particles of hydrophilic diluent dissolve in gastrointestinal fluids leaving a porous mass of drug



Gastrointestinal fluids can penetrate porous mass



Dissolution of drug occurs only from surface of plug-shaped mass. Relatively low rate of dissolution



Effective surface area of drug and hence dissolution rate is increased

Fig. 20.3 • Diagrammatic representation of how a hydrophilic diluent can increase the rate of dissolution of a poorly soluble, hydrophobic drug from a hard gelatin capsule.

Effects of Excipients

- Diluents, can increase BA or decrease by increasing hydrophobicity or complexation.
- Surfactants (solubilizing, suspending or emulsifying agent), can enhance or retard the rate of absorption.
- Lubricants can decrease BA.
- Disintegrants ?
- Viscosity enhancers, may decrease BA by complexation with drug.

Assessment of Bioavailability

- The measurement of bioavailability gives the net result of effects of the release of drug into solution in the physiological fluids at the site of absorption, its stability in those physiological fluids, its permeability and its pre-systemic metabolism on the rate and extent of drug absorption by:

(following the concentration-time profile of drug in a suitable physiological fluid).

- The concentration-time profile also gives information about other pharmacokinetic parameters, such as the distribution and elimination of the drug.
- The methods of assessing BA, involves the construction of a blood plasma concentration-time curve and cumulative urinary drug excretion curves.

Plasma concentration-time curves

- When a single dose of a drug is administered orally to a patient, serial blood samples are withdrawn and the plasma assayed for drug concentration at specific time points after administration.
- This enables a plasma concentration-time curve to be constructed.

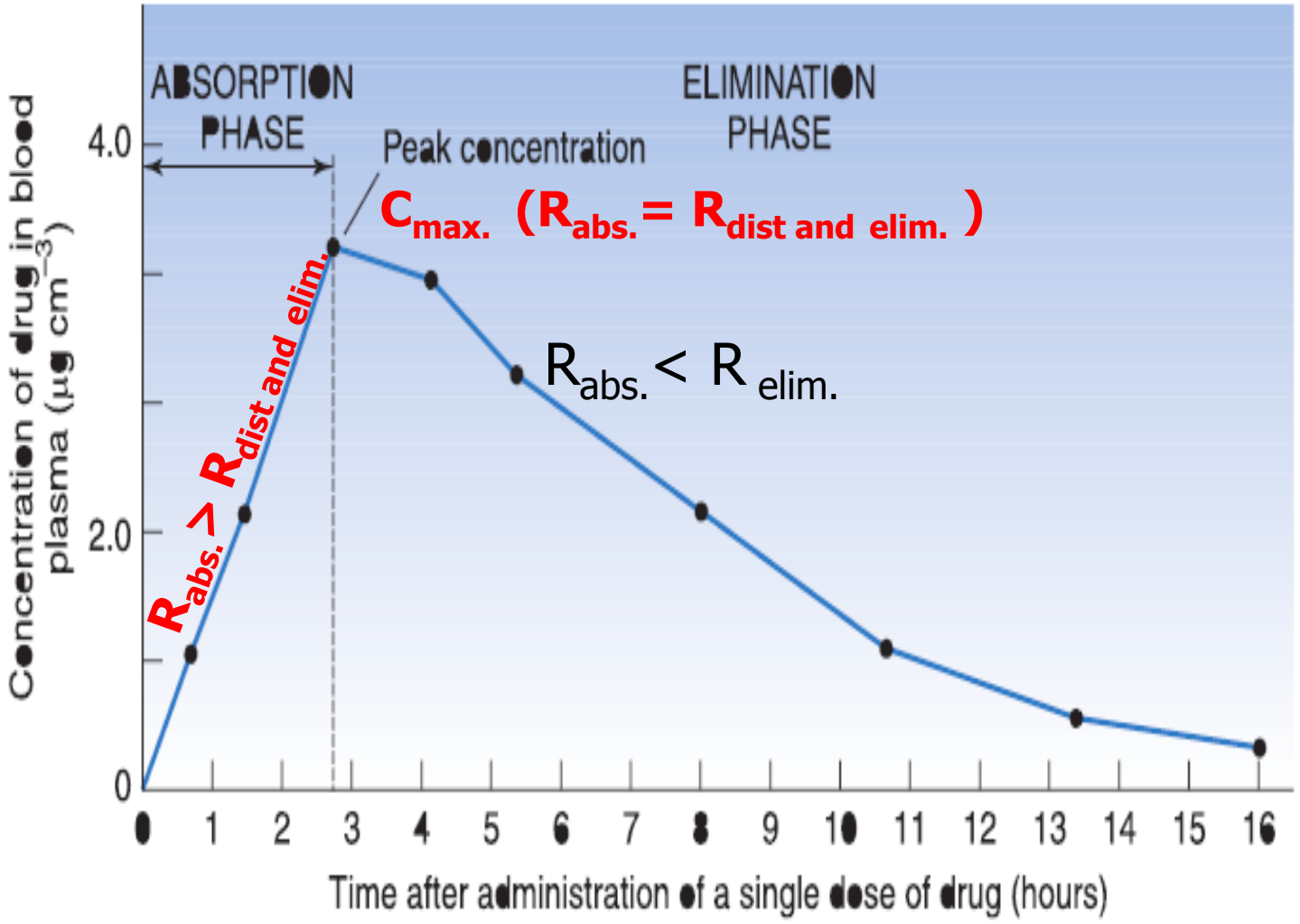


Fig. 21.8 • A typical blood plasma concentration-time curve obtained following the peroral administration of a single dose of a drug in a tablet.

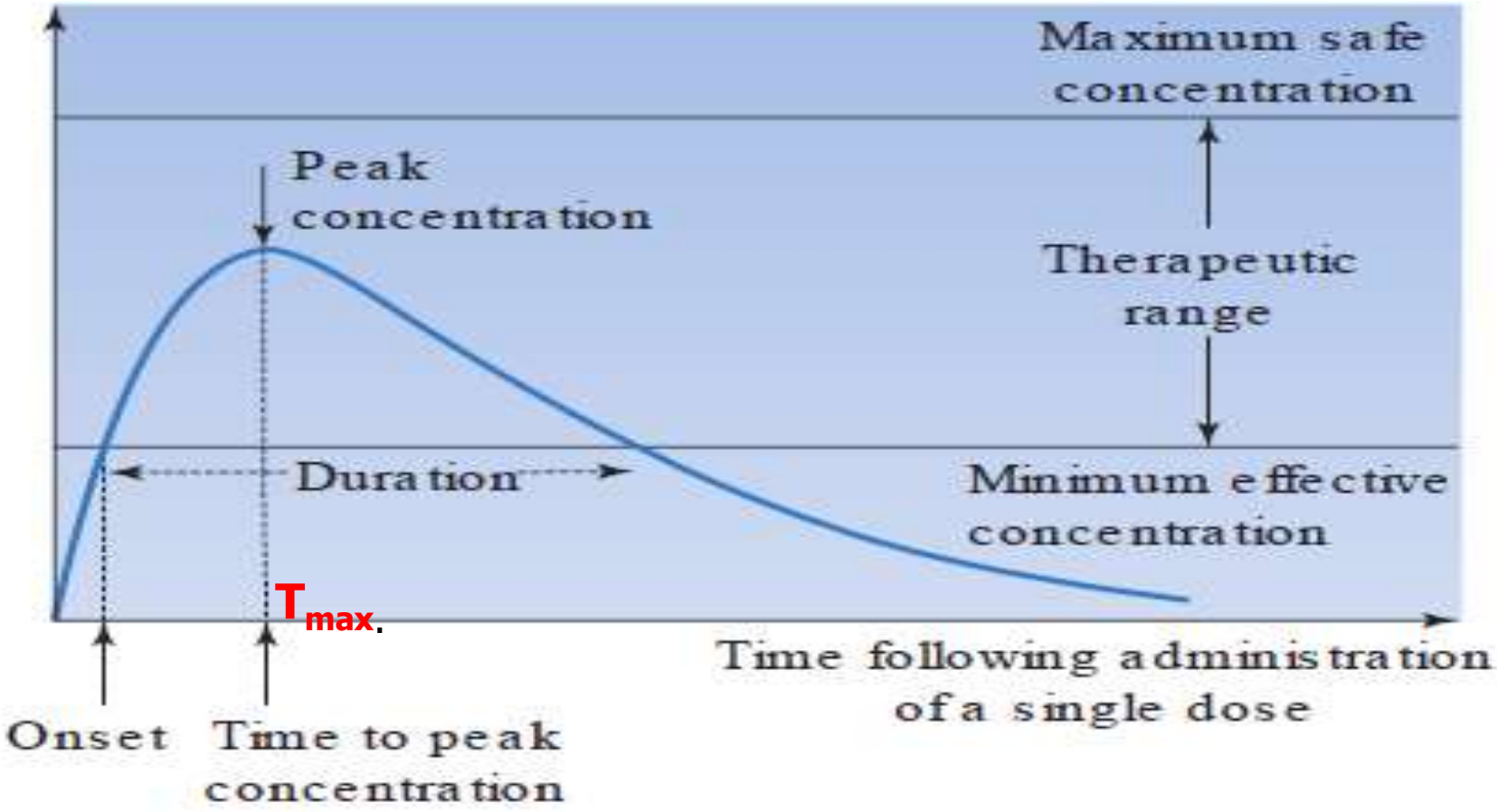


Fig. 21.9 • Relationship between the plasma concentration-time curve obtained following a single extravascular dose of a drug and parameters associated with the therapeutic or pharmacological response.

What is the meaning of AUC ?

Use of plasma concentration-time curves in bioavailability studies:

- To explain that, the administration of single equal doses of three different formulations, A, B and C of the same drug to the same healthy individual by the same route of administration on three separate occasions can be considered.

- As assumptions:

1) Sufficient time is allowed to elapse between the administration of each formulation such that the systemic circulation contained no residual concentration of drug and no residual effects from any previous administrations.

2) The kinetics and pattern of distribution of the drug, its binding phenomena, the kinetics of elimination and the experimental conditions under which each plasma concentration-time profile is obtained are the same on each occasion.

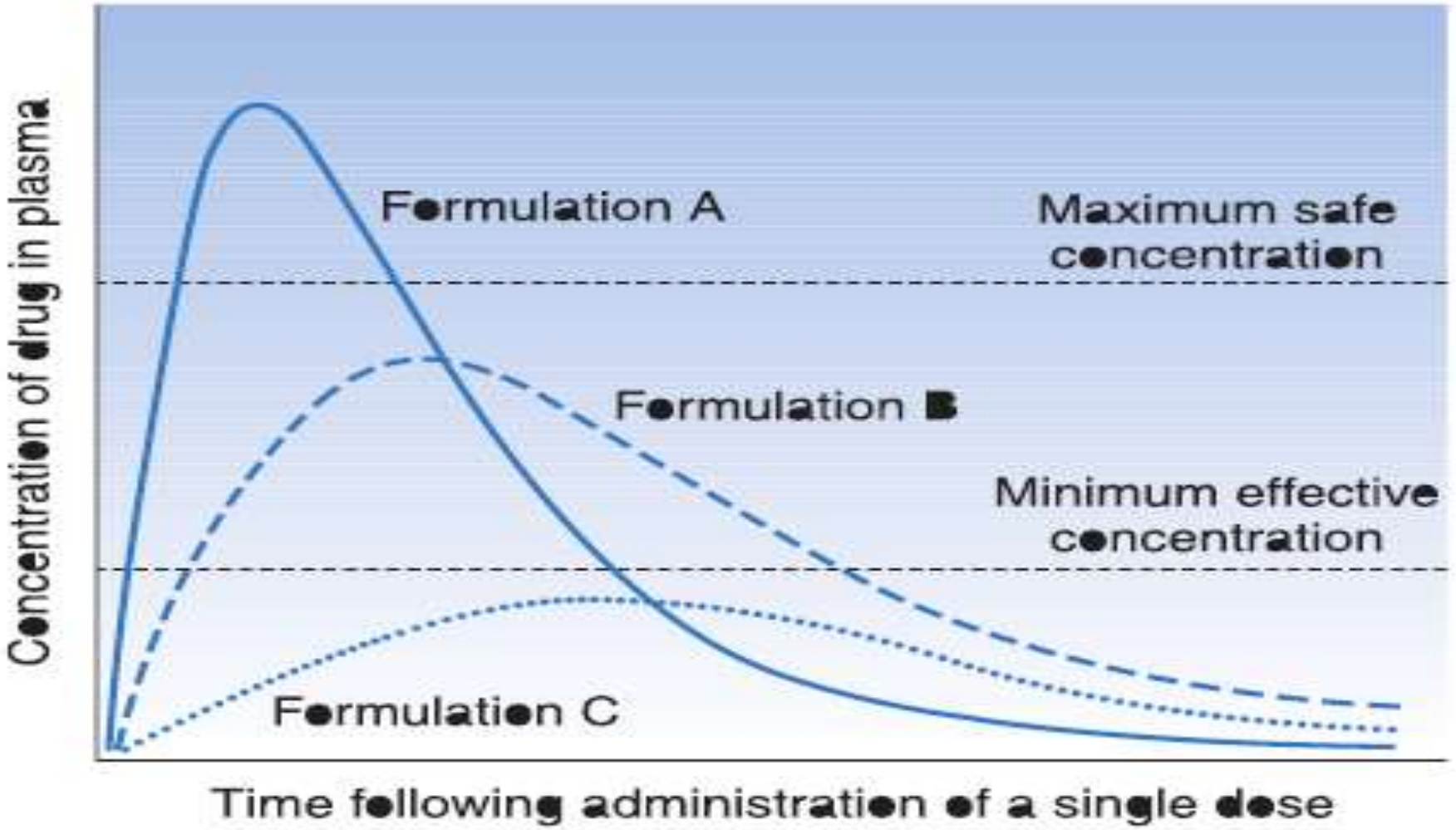


Fig. 21.10 • Plasma concentration-time curves for three different formulations of the same drug administered in equal single doses by the same extravascular route.

The differences between the three curves are attributed solely to differences in the rate and/ or extent of absorption of the drug from each formulation.

- This simple hypothetical example illustrates how differences in bioavailability exhibited by a given drug from different formulations can result in a patient being either over-, under- or correctly medicated.

- It is important to realize that the study of bioavailability based on drug concentration measurements in the plasma (or urine or saliva) is complicated by the fact that such concentration-time curves are affected by factors other than the biopharmaceutical factors of the drug product itself.(Explain that?)

Cumulative urinary drug excretion curves

- Measurement of the concentration of intact drug and/ or its metabolite(s) in the urine can also be used to assess BA.
- Measurements involving metabolite levels in the urine are only valid when the drug in question is not subject to metabolism prior to reaching the systemic circulation.

- The assessment of BA by urinary excretion is based on the assumption that the appearance of the drug and/ or its metabolites in the urine is a function of the rate and extent of absorption.
- The drug and/ or its metabolites are extensively excreted in the urine, and where the rate of urinary excretion is proportional to the concentration of the intact drug in the blood plasma.

- **This proportionality does not hold if:**

1) The drug and/or its metabolites are excreted by an active transport process into the distal kidney tubule.
2) The intact drug and/or its metabolites are weakly acidic or weakly basic (i.e. their rate of excretion is dependent on urine pH).
3) The excretion rate depends on the rate of urine flow.

- The important parameters in urinary excretion studies are the cumulative amount of intact drug and/ or metabolites excreted and the rate at which this excretion takes place.

- A cumulative urinary excretion curve is obtained by collecting urine samples (resulting from the total emptying of the bladder) at known intervals after a single dose of the drug has been administered.

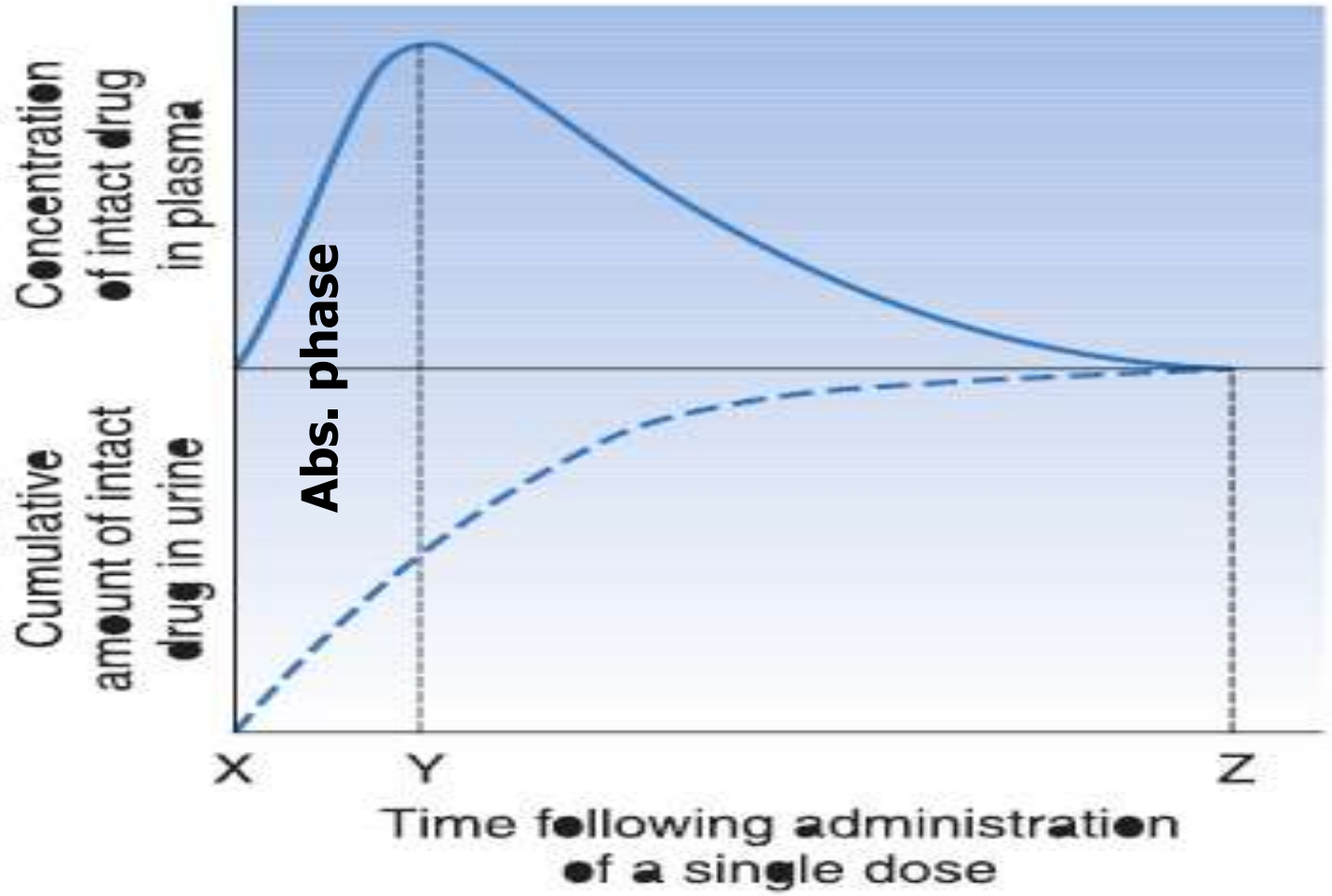


Fig. 21.11 • Corresponding plots showing the plasma concentration-time curve (upper curve) and the cumulative urinary excretion curve (lower curve) obtained following the administration of a single dose of a drug by the peroral route.

Use of urinary drug excretion curves in bioavailability studies:

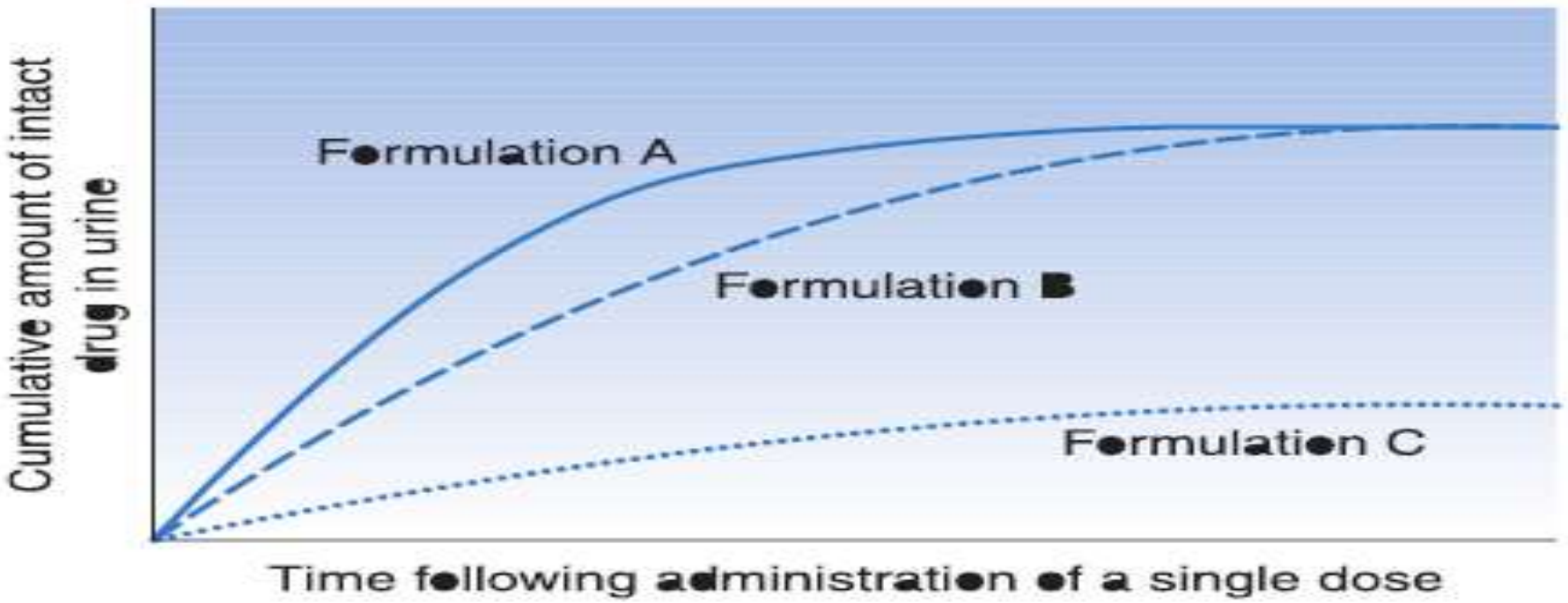


Fig. 21.12 • Cumulative urinary excretion curves corresponding to the plasma concentration-time curves shown in Fig. 21.10 for three different formulations of the same drug administered in equal single doses by the same extravascular route.

Absolute Bioavailability

- The absolute bioavailability of a given drug from a dosage form is the fraction (or percentage) of the administered dose which is absorbed intact into the systemic circulation.

- Absolute bioavailability may be calculated by comparing the total amount of intact drug that reaches the systemic circulation after the administration of a known dose of the dosage form via a route of administration, with the total amount that reaches the systemic circulation after the administration of an equivalent dose of the drug in the form of an intravenous bolus injection.

- An intravenous bolus injection is used as a reference to compare the systemic availability of the drug administered via different routes.??

For equivalent doses of administered drug:

$$\text{absolute bioavailability} = \frac{(AUC_T)_{abs}}{(AUC_T)_{iv}} \qquad (21.3)$$

- If different doses of the drug are administered by both routes, a correction for the sizes of the doses can be made as follows:

$$\text{absolute bioavailability} = \frac{(AUC_T)_{abs} / D_{abs}}{(AUC_T)_{iv} / D_{iv}} \qquad (21.4)$$

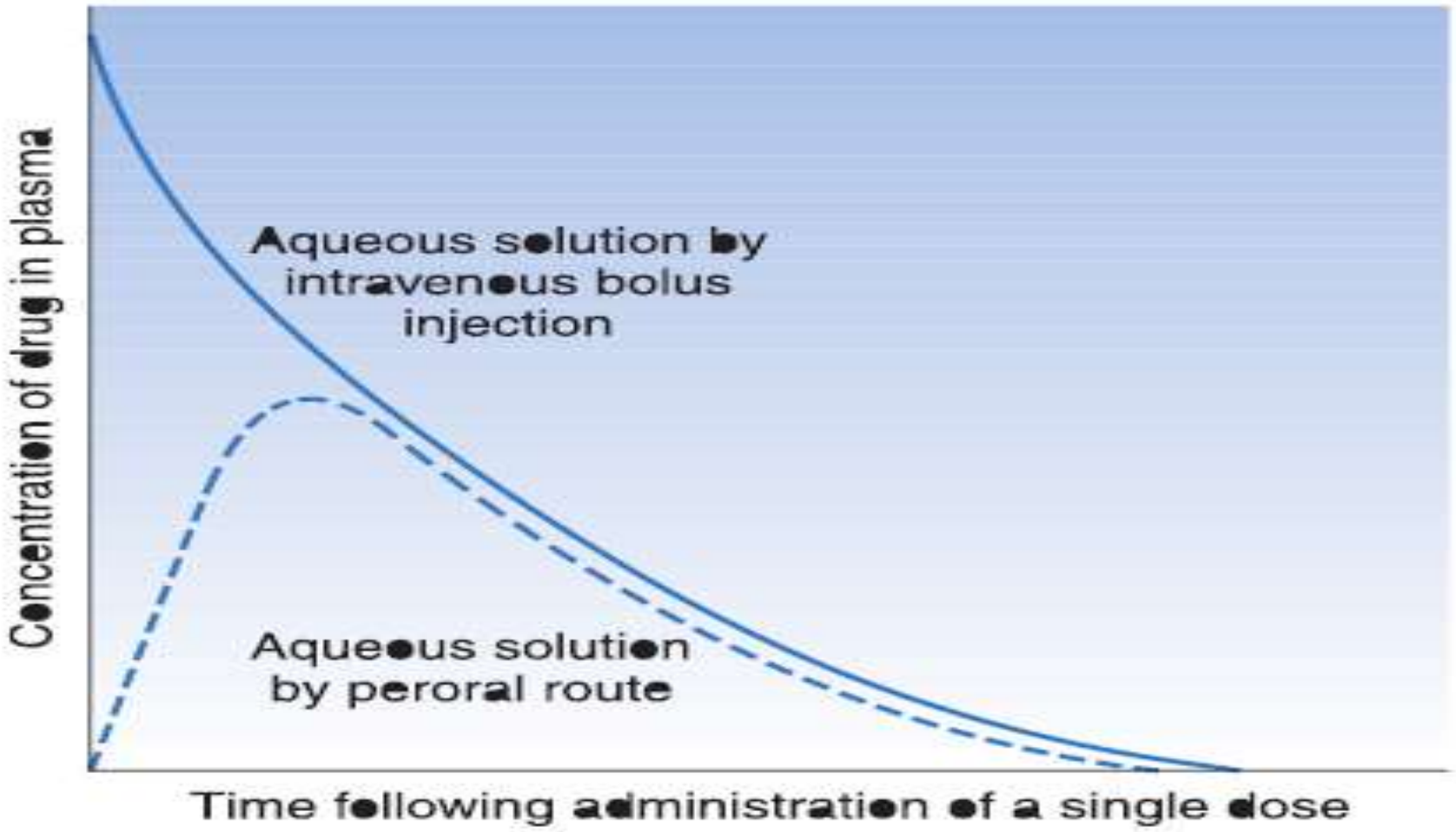


Fig. 21.13 • Typical plasma concentration-time curves obtained by administering equivalent doses of the same drug by intravenous bolus injection and by the peroral route.

Depending on urinary excretion data

For equivalent doses of administered drug:

$$\text{absolute bioavailability} = \frac{(X_u)_{abs}}{(X_u)_{iv}} \qquad (21.5)$$

- Where (Xu)abs and (Xu)iv are the total cumulative amounts of unchanged drug ultimately excreted in the urine following administration of equivalent single doses of drug via an absorption site and as an intravenous bolus injection, respectively.

If different doses of drug are administered:

$$\text{absolute bioavailability} = \frac{(X_u)_{abs} / D_{abs}}{(X_u)_{iv} / D_{iv}} \qquad (21.6)$$

Relative bioavailability

- In the case of drugs that cannot be administered by intravenous bolus injection, the relative (or comparative) bioavailability is determined rather than the absolute bioavailability.
- In this case, the bioavailability of a given drug from a 'test' dosage form is compared to that of the same drug administered in a 'standard' dosage form.

- The relative bioavailability of a given drug administered at equal doses of a test dosage form and a recognized standard dosage form, respectively, by the same route of administration to the same subject on different occasions may be calculated from the corresponding plasma concentration-time curves as follows:

$$\text{relative bioavailability} = \frac{(AUC_T)_{test}}{(AUC_T)_{standard}} \qquad (21.7)$$

- When different doses of the test and standard dosage forms are administered, a correction for the size of dose is made as follows:

$$\text{relative bioavailability} = \frac{(\text{AUC}_\text{T})_\text{test} \,/\, D_\text{test}}{(\text{AUC}_\text{T})_\text{standard} \,/\, D_\text{standard}} \qquad (21.8)$$

- Urinary excretion data may also be used to measure relative bioavailability as follows:

$$\text{relative bioavailability} = \frac{(X_\text{u})_\text{test}}{(X_\text{u})_\text{standard}} \qquad (21.9)$$