The concept of bioavailability. Pharmacokinetic parameters

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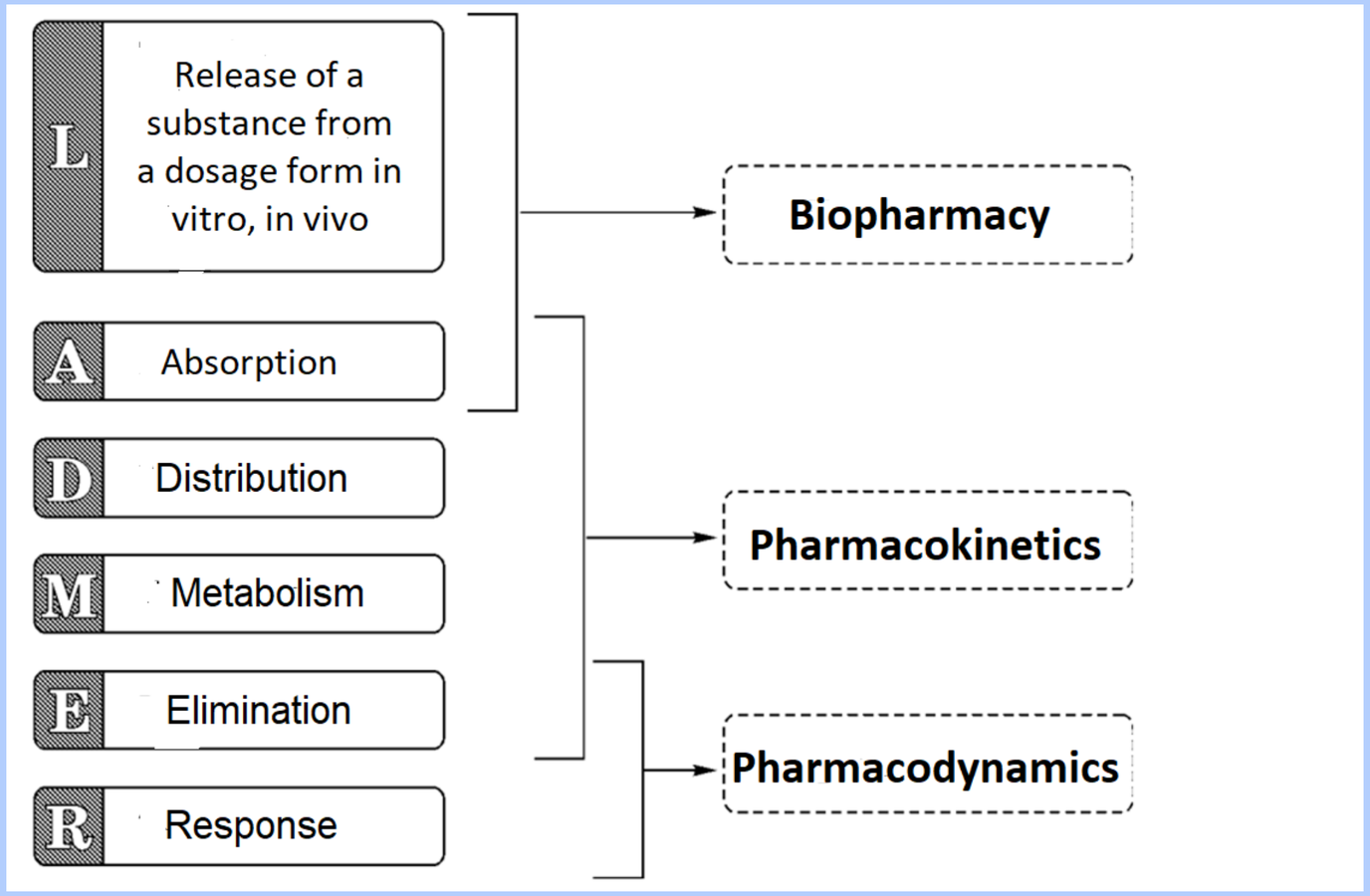


General term characterizing individual areas of drug interaction with the body (Liberation, Absorption, Distribution, Metabolism, Elimination, Response)

Bioavailability of determining the relative rate of absorption of a pharmaceutical substance (API) that has reached the degree of reaching the systemic circulation (degree of bioavailability) and the speed with which this process occurs (absorption rate), as well as the duration of its stay at the source of origin.

The concept of bioavailability was recognized by the XVII WHO atmosphere in 1974.

Degree of bioavailability

- **The degree of bioavailability** is the ratio of the amount of unchanged API absorbed and detected in the blood after its administration in the form of an investigational dosage form to its amount in the blood after administration in the standard dosage form, expressed as a percentage:

Degree of BA= B/A x 100 %

B – the amount of API in the blood after administration in the study dosage form, mg

A - the amount of API in the blood after administration in the standard dosage form, mg

The bioavailability study answers the questions:

- What part of the dose of the pharmaceutical substance was absorbed;
- How fast was the absorption;
- How long the pharmaceutical substance has been in the body;
- In what concentration of the pharmaceutical substance was distributed in the internal environment of the body.

Absolute bioavailability

- **Absolute bioavailability (F, %)** is used to estimate the total amount of API from a given drug in the patient's blood, compared with a solution of the same substance administered intravenously.

$$F = \frac{[AUC]po \cdot dose_{iv}}{[AUC]iv \cdot dose_{po}}$$

[AUC] – area under the pharmacokinetic curve

dose – API dosage

po – orally

iv - intravenously

As a standard dosage form, when determining the absolute bioavailability, a solution for intravenous administration is used, which provides an immediate and complete supply of API to the systemic circulation.The annotations on the medicinal product indicate the absolute bioavailability. For oral drugs, it is considered optimal in the range of 40 - 60%.

Relative bioavailability

- **Relative bioavailability (RF, %)** is the ratio (in %) of the amount of API absorbed after extravascular administration in the studied dosage form to the amount of API that entered the systemic circulation after extravascular administration at the same dose

$$\mathrm{R}F = \frac{[AUC]_A \cdot dose_B}{[AUC]_B \cdot dose_A}$$

Relative bioavailability is measured against a reference product by the same route of administration.

Total bioavailability

- For drugs that are extensively metabolized by the liver when taken orally, the concept of total bioavailability is used.

- ***Total bioavailability*** is the fraction of an ingested dose of a medicinal product that reaches the systemic circulation unchanged and in the form of metabolites formed during absorption as a result of first pass metabolyme ("First pass effect")

Methods for determining bioavailability

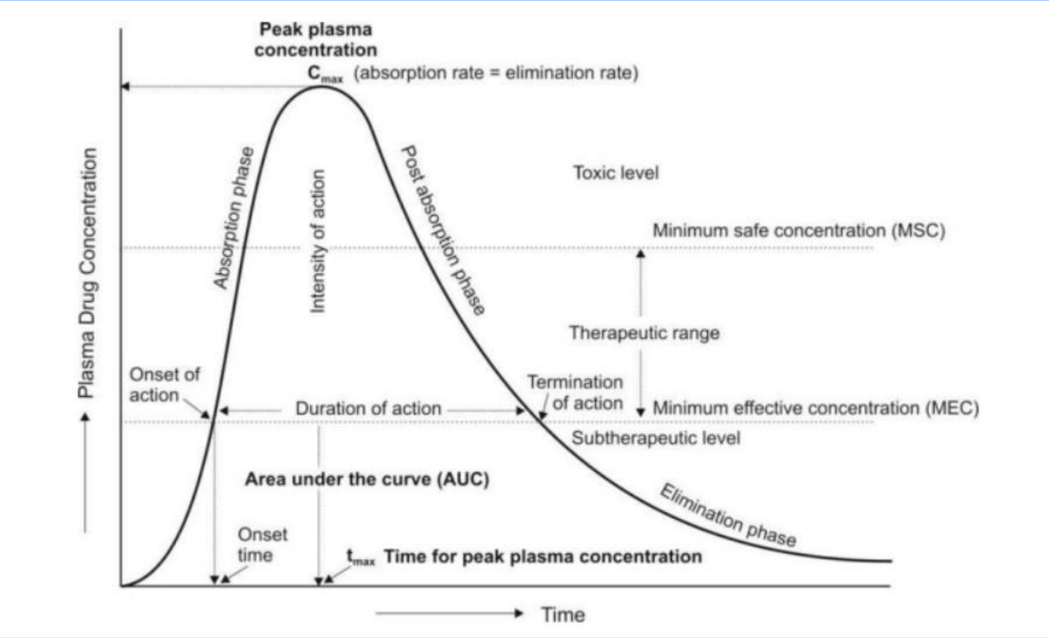
- ***Pharmacodynamic method -*** based on the measurement of pharmacodynamic or biochemical reactions to a drug substance or its active metabolites (complicated, destructive).

- ***Pharmacokinetic method -*** measuring the concentration of a drug or its metabolites in a biofluid (blood plasma, urine) over time. Based on the data obtained, graphs are built that reflect the kinetics of the content of the drug or active metabolite in the biofluid over time, and bioavailability is calculated using pharmacokinetic methods.

Pharmacokinetic method for determining bioavailability

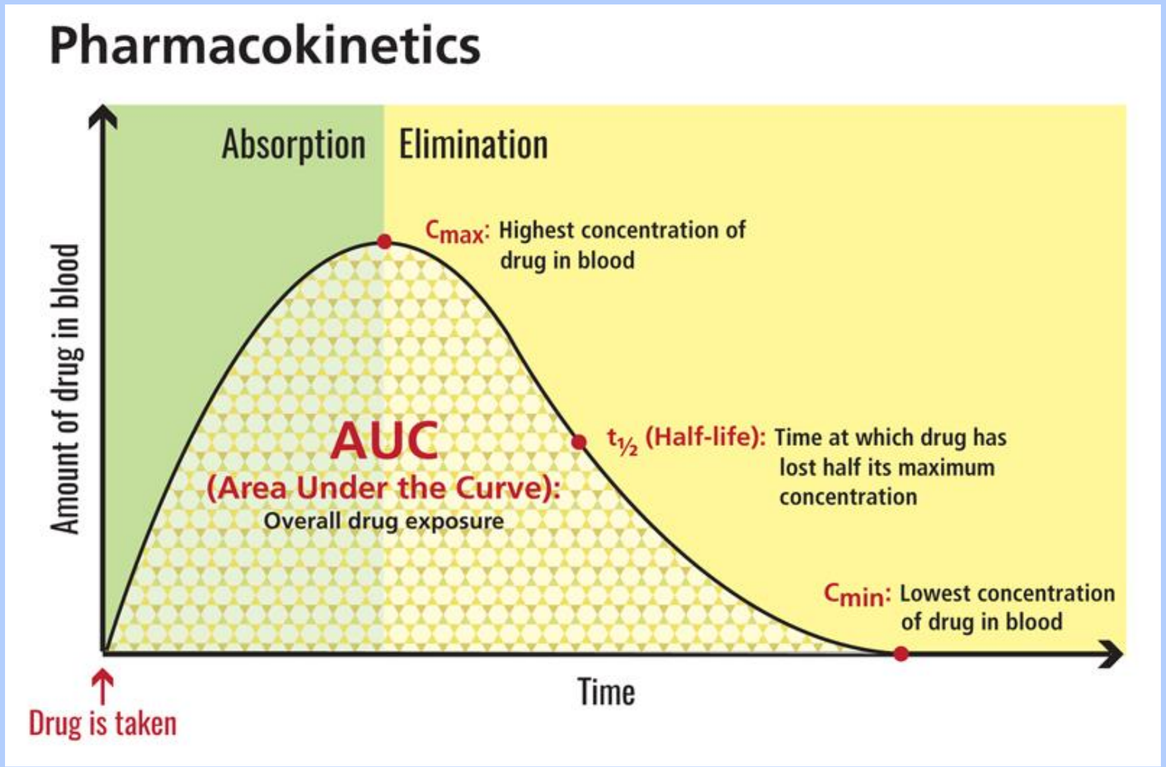
- Measurement of the change in the concentration of API in blood plasma over time by determining the total amount of API or its metabolites excreted in the urine after single or repeated doses.

- Bioavailability indicators are considered in terms of the maximum plasma concentration (Cmax), the time to reach this concentration (Tmax) and the area under the pharmacokinetic curve (area under curve - AUC), after using the drug at the same dose under the same conditions.



Bioavailability indicators

- The maximum (peak) concentration of the drug in the blood;
- Time to reach maximum concentration;
- The area under the curve of changes in the concentration of a drug in serum or plasma over time.



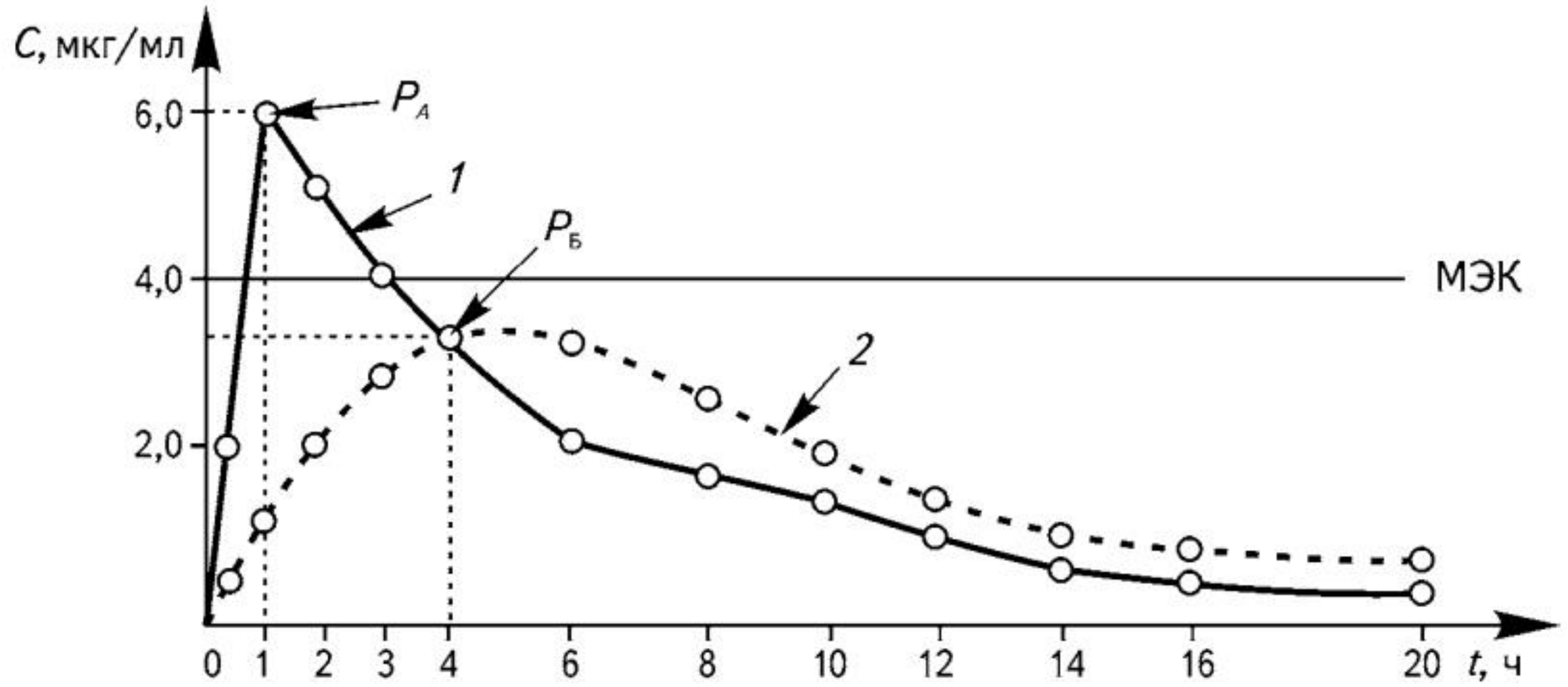


Рис. 3.2. Динамика концентрации (*C*) лекарственного вещества после применения его в двух лекарственных формах:

1 — лекарственная форма А; *2* — лекарственная форма Б; *P* — пик концентрации лекарственного вещества; МЭК — минимальная эффективная концентрация

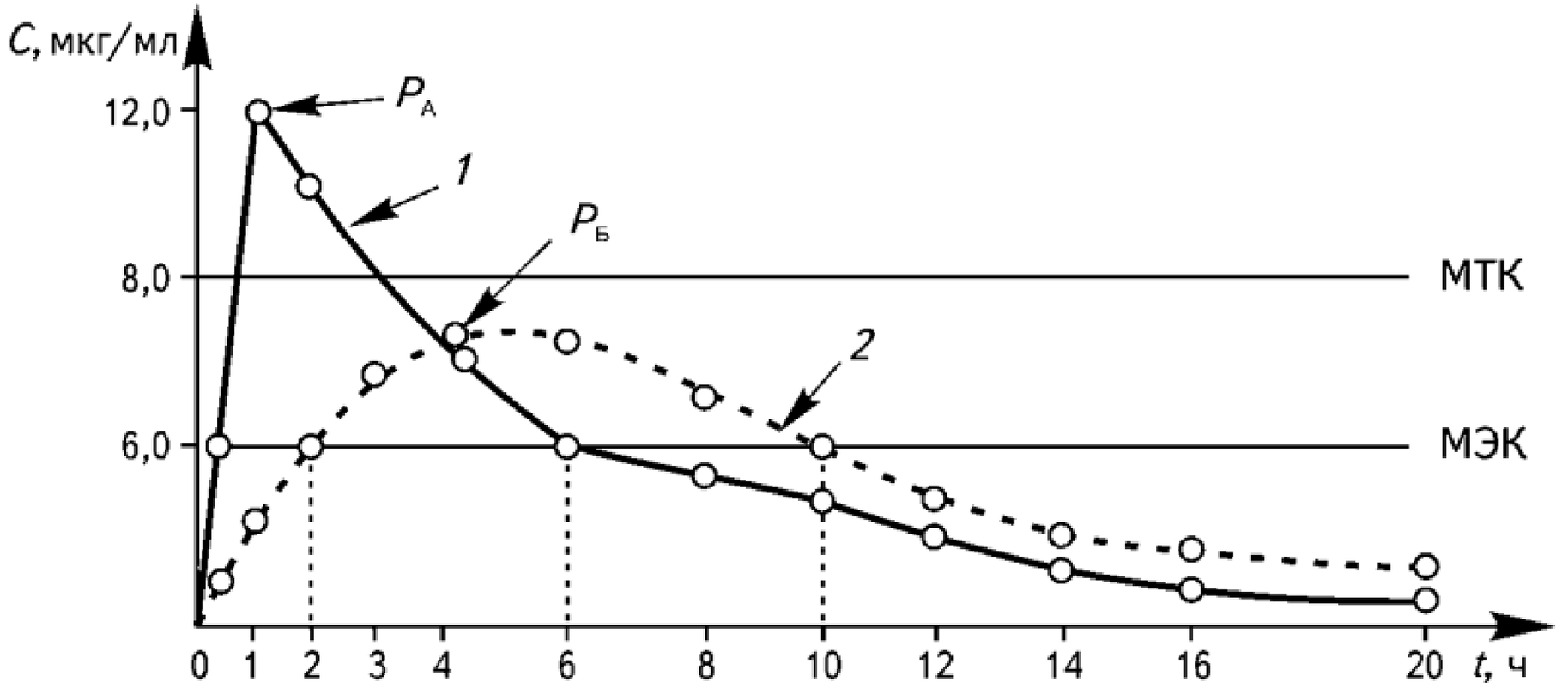


Рис. 3.3. Определение минимальной токсической концентрации (МТК) и минимальной эффективной концентрации (МЭК) лекарственного вещества по динамике его концентрации в крови при применении в двух лекарственных формах (А и Б):

1 — лекарственная форма А; *2* — лекарственная форма Б; *P* — пик концентрации лекарственного вещества; $AUC_А$ = 34,4 (мкг/мл)·ч, $AUC_Б$ = 34,2 (мкг/мл)·ч

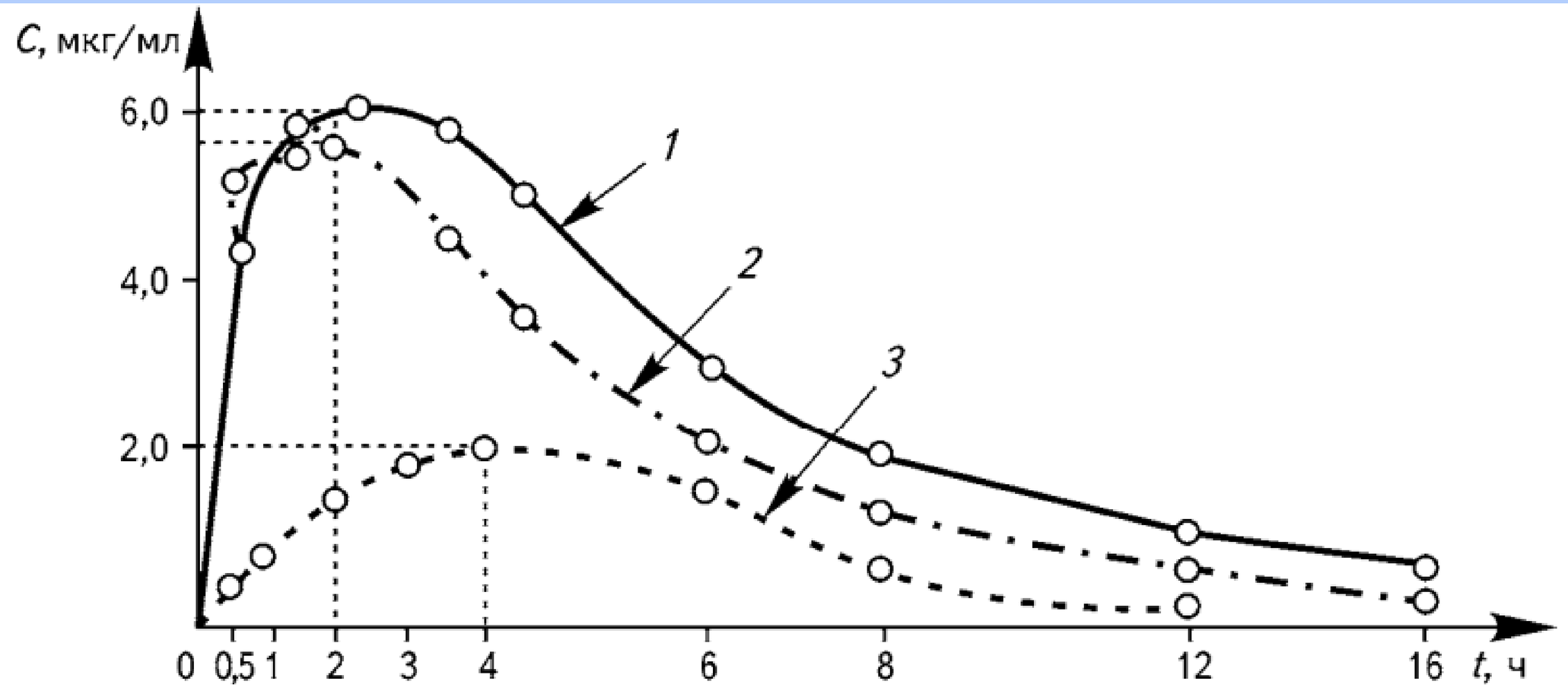


Рис. 3.4. Относительная биодоступность лекарственного вещества при применении его в трех лекарственных формах:
1 — лекарственная форма А; *2* — лекарственная форма Б; *3* — лекарственная форма В; $AUC_A = 39,9$ (мкг/мл)·ч, $AUC_Б = 32,2$ (мкг/мл)·ч, $AUC_В = 14,0$ (мкг/мл)·ч

Factors affecting bioavailability

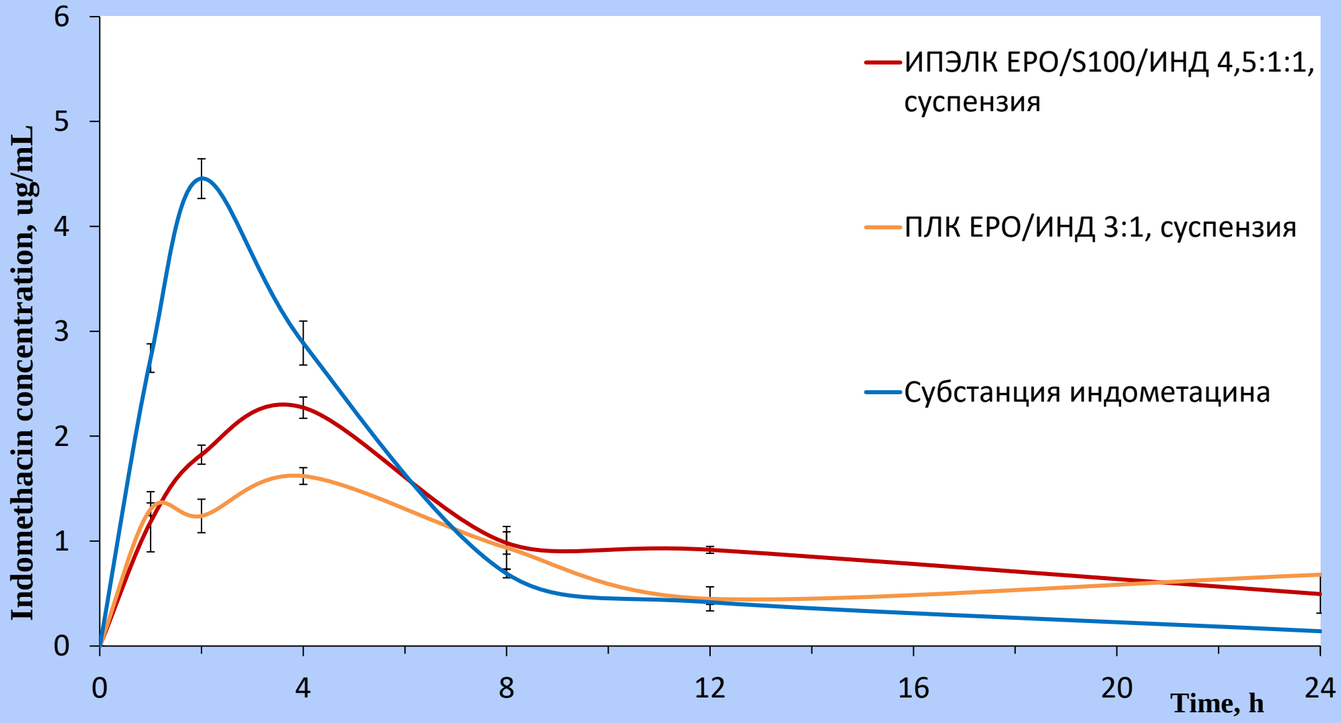
- The route of administration of the dosage form
- Composition and temperature of food
- The nature of the liquid used to drink the medicines
- Influence of foods (diet)
- Body and environment temperature
- Magnetic field and meteorological factors
- Age and gender of the person
- biological rhythms
- Pathological processes and individual characteristics of the organism

Factors affecting bioavailability

- Alcohol
- Smoking
- Taking other drugs (drug interactions)

Determination of bioavailability

Bioavailability is determined only in vivo, in laboratory animals, in clinical trials in humans.



Determination of pharmacokinetic parameters was carried out on male Chinchilla rabbits with an average weight of 3.76 kg.

In the morning, on an empty stomach, rabbits were orally administered PLA EPO/IND 3:1 and IPELK EPO/S100/IND 4.5:1:1 as a suspension or as tablets with a dosage of 25 mg of indomethacin.

After 1;2;4;8;12 and 24 hours, blood samples were taken from the marginal ear vein. Samples were centrifuged at 1000 rpm (4 min). To a 500 µl blood plasma sample, 500 µl of acetonitrile was added to precipitate proteins.

The resulting suspension was stirred on an IKA vortex for 2 minutes, after which it was stirred on a shaker for 2 minutes. The precipitates obtained were centrifuged at 10,000 rpm in a centrifuge for 10 minutes.

The concentration of indomethacin in the supernatant was determined by HPLC.