INTRODUCTION

The most part (84%) of drugs available at the pharmaceutical market in the USA and Europe represents solid oral dosage forms. Bioavailability is one of the main parameters characterizing drug efficiency. It is also the main parameters during determination of equivalence of generic preparations to the referent ones.

Now within construction, screening, selection and introduction of innovation preparations it is recommended to predict and (ideally) to determine bioavailability of a prodrug candidate during early stages of this process.

Here we consider theoretical principles for determination and prediction of bioavailability according to the Biopharmaceutical Classification System (BCS). Certain attention has also been paid to other systems supplemented with new descriptors.

1. PHARMACOKINETIC CHARACTERISTICS OF BIOAVAILABILITY

Bioavailability is the degree to which, or the rate at which an active pharmaceutical ingredient (API) from corresponding drug dosage form and at the targeted place of administration in systemic circulation becomes available in the biophase (21 CRF 320.1). Such definition reflects relative character of the notion of biological availability of drugs.

In practice bioavailability in vivo is defined by the formula:

\[ F = \frac{AUC_{ev}}{AUC_{iv}} \]  

where \( AUC_{ev} \) and \( AUC_{iv} \) are corresponding parameters of areas under curves obtained during extravasal and intravasal way of drug administration (expressed as mmol h \( l^{-1} \), mmol min \( l^{-1} \), \( \mu g \) h \( l^{-1} \), \( \mu g \) min \( l^{-1} \), etc.)

Mathematically, AUC represents an integral \( C(t) \) of all time values from zero to infinity in time:

\[ AUC = \int_{0}^{\infty} C(t) dt. \]  

In pharmacokinetics this value is also defined as zero order statistical moment. Definition from zero to infinity means that total area under the curve is evaluated. However, under experimental conditions it is better to compare areas limited by curves and the level of bioavailability.

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1 Here and in other places we cite the reference 21 CFR 320—Bioavailability and bioequivalence requirements http://www1.va.gov/oro/apps/compendium/Files/21CFR320.htm.
minimal effective concentration of a drug rather than total areas under corresponding curves [1].

There are special model-dependent and model-independent methods for AUC calculation [2].

In dependence of goals of particular study F (expressed as percent) may be absolute or relative values.

Absolute bioavailability is a proportion of unaltered API, which has reached systemic blood circulation. Theoretically this value may be zero (for API, which cannot be absorbed from the administration place) and 100 (for a drug, which totally entered circulation). Most intravenously administered drugs are characterized by F values of 100%.

Relative bioavailability is relative bioavailability for two drug dosage forms containing similar API, administered in similar (but not intravenous) way. In this case

\[ F = \frac{AUC_{test}}{AUC_{referent}}. \] (3)

The drug dosage forms are considered as bioequivalent, when the dependences concentration versus time of experiment coincide (provided that a 90% confidential interval for a geometrical mean value calculated for individual ratios of logarithmically transformed AUC mean values is within the range 0.80–1.25 for test and referent preparations).

Bioavailability is inseparable part of common pharmacological studies known in the literature as ADME (Absorption, Distribution, Metabolism, Elimination).

In pharmacological studies absorption is often identified as bioavailability. In some cases this is true, however, some their differences should be also taken into consideration (Table 1).

Bioavailability mainly depends on intestinal and hepatic clearance of API. In the case when clearance rate depends on blood API concentration absorption and bioavailability are identical. However, if clearance process employs active secretion or metabolic pathways and it becomes saturable the pharmacokinetic dependence becomes nonlinear. In this case changes in absorption is not accompanied by proportional change in bioavailability.

In general, the AUC value is related to other fundamental pharmacokinetic parameters. Firstly, to AUMC (area under the moment curve); this is total area under the curve of multiplication of time by API concentration in the body from the moment of its administration to the body up to total elimination. Secondly, to MRT (mean retention time)

\[ MRT = \frac{AUMC}{AUC}. \] (4)

Thirdly, AUC value is reversibly proportional to total clearance (Cl). In the case of linear distribution in the body the AUC value is proportional to the amount (dose) of API administered to the body.

Figure 1 illustrates usefulness of the considered information for clinical pharmacology.

Following pharmacological characteristic features [1] we may conclude that efficiency (E) of API depends on an administered dose (D) and in the simplest case it may be written as:

\[ E = f(D). \] (5)

However, according to Fig. 1, the dosage regime (which dose and time interval between administration) depends on pharmacokinetic parameters and so some variables must be included in the right part of equation (5):

\[ E = f(D, t, F, Vd, Cl). \] (6)

Symbols of the right part of equation (6) indicate the existence of complex interrelations between pharmacodynamic and pharmacokinetic parameters during API model construction. Elucidation of links between these parameters gives possibility to analyze and even regulate the effect (E) value by influencing certain parameters, for example, F.

In pharmacology and pharmacy two important problems are also associated with bioavailability.

(1) The main reasons of unsuccessful attempts to introduce innovation preparations into medical practice are [3]: low bioavailability (39%), toxicity (21%), lack of expected efficiency (30%), commercial reasons

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**Table 1.** Characteristics of absorption and bioavailability processes

<table>
<thead>
<tr>
<th>Absorption</th>
<th>Bioavailability</th>
</tr>
</thead>
<tbody>
<tr>
<td>Strictly corresponds to API dose</td>
<td>Corresponds to an API dose and clearance value</td>
</tr>
<tr>
<td>In some cases corresponds to a therapeutic effect</td>
<td>Strictly corresponds to therapeutic effect</td>
</tr>
<tr>
<td>Depends on permeability of corresponding biomembranes (enterocytes)</td>
<td>Depends on both API entrance to blood circulation and elimination from it</td>
</tr>
</tbody>
</table>

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**Fig. 1.** Interrelationship between the main pharmacokinetic parameters.