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# Pharmaceutical Usefulness of Biopharmaceutics Classification System: Overview and New Trend

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**ABSTRACT** − Since the introduction of the biopharmaceutics classification system (BCS) in 1995, it has viewed as an effective tool to categorize drugs in terms of prediction for bioavailability (BA) and bioequivalence (BE). The BCS consist of four drug categories: class I (highly soluble and highly permeable), class II (low soluble and highly permeable), class III (highly soluble and low permeable) and class IV (low soluble and low permeable), and almost all drugs belong to one of these categories. Likewise, classifying drugs into four categories according to their solubility and permeability is simple and relatively not controversial, and thus the FDA adopted the BCS as a science-based approach in establishing a series of regulatory guidance for the industry. Actually, many pharmaceutical companies have gained a lot of benefits, which directly connect to cost loss and failure decrease in the early stage of drug development. Recently, instead of solubility, using dissolution characteristics (e.g. intrinsic dissolution rate) have provided an improvement in the classification in correlating more closely with *in vivo* drug dissolution rather than solubility by itself. Furthermore, a newly modified-version of BCS, biopharmaceutics drug disposition classification system (BDDCS), which classify drugs into four categories according to solubility and metabolism, has been introduced and gained much attention as a new insight in respect with the drug classification. This report gives a brief overview of the BCS and its implication, and also introduces the recent new trend of drug classification.

**Key words** − biopharmaceutics classification system (BCS), solubility, permeability, bioavailability, bioequivalence

Recently, a number of drug molecules have been synthesized or discovered, and among them, some promising candidates enter into drug pipelines for further *in vitro*/*in vivo* testing through a variety of screening processes. At an initial drug development stage, a proper categorization based on the physicochemical nature of drug molecules is essential for better understanding in the view of pharmacokinetics and biopharmaceutics, and this process obviously help to not only increase success probability to develop a final drug product, but also avoid the additional cost loss due to performing clinical tests in human subjects.

Since the biopharmaceutics classification system (BCS) was introduced by Amidon et al. in 1995, it has been eagerly used as an effective prediction parameter to relate the physicochemical characteristics of an orally-available drug substance to *in vivo* bioavailability (Amidon et al., 1995). It categorizes drugs into four classes according to their solubility and permeability, and thus almost all drugs belong to one of these four classes. This system presented a new paradigm to regulatory practices associated with bioavailability (BA) and bioequivalence (BE) issues. Classifying drugs according to the BCS has resulted in an improved SUPAC-IR guidance, a dissolution guidance, and an FDA guidance (Lindenberg et al., 2004; FDA guidance 2000). Especially, owing to the benefit of BCS, considerable numbers of drug products can be considered for "biowavers", i.e., approval of the products based on *in vitro* dissolution studies without *in vivo* bioequivalence studies in human subjects. Consequently, unnecessary human clinical studies can be avoided and the costs for generic products can be significantly decreased. In 2000, the Food and Drug Administration (FDA) utilized the BCS system in an attempt to give waiver of *in vivo* BA and BE tests of immediate-release solid dosage forms for class I (high solubility/high permeability) drugs, if such drug products show rapid dissolution pattern (FDA guidance 2000).

This report gives a brief overview of the BCS: its pharmaceutical implication, its application to *in vivo* studies including *IVIVC* consideration, and introduces a new trend of its

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modest revision for the classification according to dissolution, drug disposition and metabolism.

## General Aspects

The BCS approach is based on the drug solubility and the drug permeability across the gastrointestinal tract, and the overall description can be expressed by Fick's first law applied to a mucosal membrane as follows:

$$J_w = P_w \cdot C_w = dM/dt \times 1/A$$

Where $J_w$ is the drug flux (mass transfer) through the intestinal wall at any position and time, $P_w$ is the permeability of the membrane, $C_w$ is the drug concentration at the intestinal membrane surface, and A is the surface area. This equation describes that such two factors of solubility and permeability are the major variables to explain the mass transport through a membrane (Löbenberg et al., 2000; Shargel et al., 2004). This approach does not deal with the formulation effect using a variety of excipients on permeability in the gut wall.

On the basis of a mass balance in the gastrointestinal (GI) tract, different quantitative approaches have been developed to predict the GI drug permeation and discussed by Yu et al (Sinko et al. 1991; Yu et al., 1996). In the BCS, three dimensionless numbers such as dose number ($D_n$), dissolution number ($Ds_n$) and absorption number ($A_n$) are defined to characterize drug substances. Such numbers are combinations of physicochemical and physiological parameters and express the basic aspect of drug absorption in the GI tract (Löbenberg et al., 2000). First, the absorption number, $A_n$, is the ratio of permeability and the gut radius times the residence time in the small intestine, which can be expressed as the ratio of residence time and absorptive time. Second, the dissolution number ($Ds_n$) is the ratio of the residence time to the dissolution time known to include solubility, diffusivity, density, and the initial particle radius of a compound and the intestinal transit time. Finally, the dose number, $D_n$, is known as the ratio of dose concentration to drug solubility (Löbenberg et al., 2000).

### Solubility

The first essential factor to classify a drug according to the BCS is to determine the equilibrium solubility of a drug under physiologic conditions. The pH of gastrointestinal tract from stomach to colon is known to be the approximate range of 1~7.5. Therefore, data for pH-solubility (in mg/ml) profiles over a pH range of 1~7.5 at 37°C should be obtained (Amidon et al., 1995; FDA guidance 2000; Yu et al., 2002). The solubility class is determined by calculating volume of an aqueous medium which is sufficient to dissolve the highest anticipated dose strength. However, solubility was typically measured in at least three times by equilibrating excess amount of drugs in aqueous media at pH values of 1.2, 4.5, and 6.8 and in deionized water in thermostated bath at 37°C for over 24 h. Particularly, the solubility of ionizable drugs is clearly dependent on such pH consideration, and may be changed remarkably on the basis of pH (Löbenberg et al., 2000). In most cases, the samples obtained are analyzed by UV-spectrophotometry or high performance liquid chromatography (HPLC).

In general, a drug substance is regarded "highly soluble" when the highest dose strength is soluble in 250 ml or less of aqueous media over a pH range of 1~7.5 at 37°C (Wu et al., 2005). This 250 mL volume is derived from typical bioequivalence study protocols that prescribe administration of a drug product to fasting human volunteers with a glass (8 ounces) of water (Shargel et al., 2004; FDA guidance 2000). Likewise, a criterion of determining high or low solubility depends on not only the apparent solubility but also the practically-used maximum administration dose. Furthermore, the relevant FDA guidance for the industry "Biowaiver of *in vivo* bioavailability and bioequivalence studies for immediate-release solid oral dosage forms based on a biopharmaceutics classification system" (FDA guidance 2000; http://www.fda.gov/cder/guidance) suggests that high solubility drugs are those with a dose (mg)/solubility (mg/ml) (D : S) ratio of < 250 mL at the same conditions mentioned above. As a result, this ratio value is used to decide whether a drug has a high solubility or not (Löbenberg et al., 2000).

### Permeability

The second necessary factor to categorize drugs by BCS is to obtain authentic permeability data from humans, but this is not easy to find because this kind of human data are usually limited. Despite this difficult problem, absorption data from the pharmacokinetics or perfusion in human subjects are primary source or choice for permeability data, and these are still preferred by the FDA (Martinez et al., 2002; Tannergren et al., 2003; Lennernas et al., 1997 and 2002; Waterbeemd et al., 1998; Fleisher et al., 1999). However, data from *in vivo* or *in situ* animal models can be also utilized in a few exceptional cases. Moreover, results in cultured cell monolayers (mostly Caco-2 cells) validated by a confirmed procedure according to the FDA biowaver guidance can be often reliable and available (Bergstrom et al, 2003; Rege et al., 2001; Tannergren et al., 2001; Taub et al., 2002). But it is known to be quite difficult to accurately assign the drug to 'high' or 'low' permeability, and thus these cell-based permeability data are usually con-

sidered in most cases as supplementary rather than the first priority information (Löbenberg et al., 2000). In general, a drug substance is considered "highly permeable" when the drug absorption extent (including metabolite) in humans is determined to be 90% or more of an administered dose strength on the basis of a mass balance determination or in comparison to an intravenous reference dose (Wu et al., 2005; FDA guidance 2000).

**Dose**

As mentioned, a simple solubility does not give a significant meaning to decide the class of drug substance in the BCS. This dose may differ from specification in the prescriptions according to countries or manufacturers. For example, drug products with the same active ingredient have different dose strength: the practically used dose of Aspirin is in the range of 100~500 mg (WHO), and moreover a very high dose prescription of 1000 mg is known to be found in Germany (Lindenberg et al., 2004). Meanwhile, glimepiride (Amaryl®) is commercially produced at a very low dose of 1 or 2 mg. Consequently, the newly modified solubility concept reflected by the practically-used dose can be a more meaningful value rather than solubility by itself.

Despite such different dose strength, in general, the highest dose (in mg) described in the WHO list of drugs is generally recommended calculate (D : S) ratio (Lindenberg et al., 2004; Wu et al., 2005). Furthermore, according to the case of FDA biowaiver guidance, the highest dose administered must be used to determine the (D : S) ratio in BCS.

**Dissolution**

The dissolution class is based on the *in vitro* dissolution rate of an immediate release drug product under specified test conditions. This process is usually intended to indicate rapid *in vivo* dissolution in association with the gastric emptying rate under fasting conditions in humans. The rapidly dissolving condition for an immediate-release drug product is considered when no less than 85% amount of drug substance dissolves within 30 minutes using USP Apparatus I at 100 rpm (Apparatus II at 50 rpm) in a volume of 900 mL or less in each of the following media: (1) 0.1 N HCl or Simulated Gastric Fluid USP without enzymes; (2) a pH 4.5 buffer; and (3) a pH 6.8 buffer or Simulated Intestinal Fluid USP without enzymes (Shargel et al., 2004; FDA guidance 2000).

## Drug Categorization According to the BCS

According to the BCS, in theoretical, drugs can be categorized as one of the four classes based on their solubility (dose considered) and human intestinal permeability. As shown in Table I, the BCS are comprised in four drug categories: class I (highly soluble and highly permeable), class II (low soluble and highly permeable), class III (highly soluble and low permeable) and class IV (low soluble and low permeable). The drugs which belong to these categories are shown to have their own unique characteristics as seen in the Table I and Figure 1.

Lindenberg et al. thoroughly searched and analyzed 130 orally administered drugs found in the WHO model list of Essential Medicines, and then assigned the drugs into the BCS class. Among them, almost 50% (61 drugs) could be classified with reliability (Lindenberg et al., 2004). More specifically, 21 drugs of these (34%) were classified as class I drugs, 10 as class II drugs (17%), 24 as class III drugs (39%) and 6 as class

**Table I.** *Drug Categorization According to Biopharmaceutics Classification System and their Basic Characteristics*

| Class | Solubility | Permeability | Comments | IVIVC expectation |
|---|---|---|---|---|
| I | High | High | Drugs rapidly dissolve and well absorbed. Bioavailability problem is not expected for immediate release drug products. | IVIVC if the dissolution rate is slower than the gastric empting rate, otherwise limited or no correlation. |
| II | Low | High | Drug is dissolution limited and well absorbed. Bioavailability is controlled by the dosage form and rate of release of the drug substance | IVIVC expected if the in vitro dissolution rate is similar to the *in vivo* dissolution rate, unless the dose is very high. |
| III | High | Low | Drug is absorption (permeability) limited. Bioavailability may be incomplete if drug is not release and dissolved within absorption window. | Limited or no IVIVC expected |
| IV | Low | Low | Difficulty in formulating a drug product that will deliver consistent drug bioavailability. An alternate route of administration may be needed. | Limited or no IVIVC expected |

Adapted and reorganized from Amidon et al., 1995; Löbenberg et al., 2000; and Shargel et al., 2004. From FDA guidance for industry: Waiver of in vivo bioavailability and bioequivalence studies for immediate release solid oral dosage forms containing certain active moieties/active ingredients based on a biopharmaceutics classification system (2000).

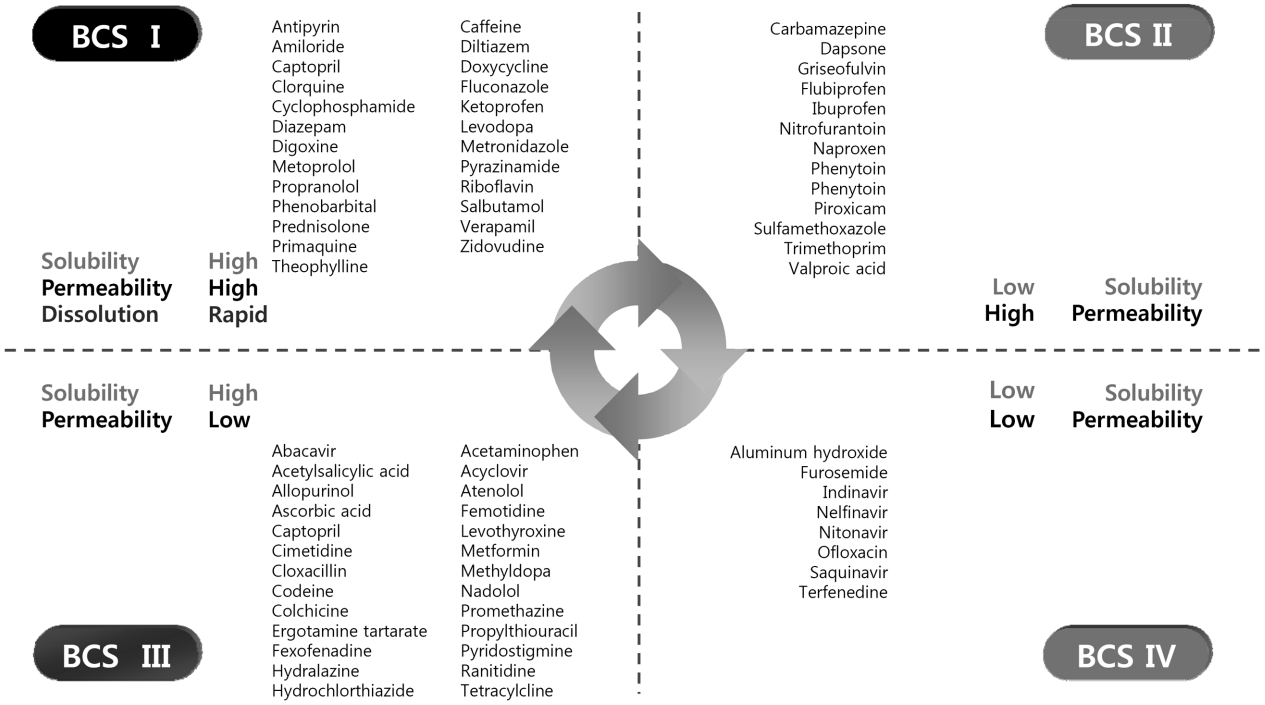


**Figure 1.** Categorization of various drugs according to biopharmaceutics classification system. The drug list was predominantly adapted from the literature (Lindenberg et al., 2004; Wu et al., 2005) and reorganized.

IV drugs (10%). In the case of a total of 89 drugs with reliable solubility data but lacking permeability data, 32 drugs of these are categorized as class I drugs (36%), 15 class II drugs (17%), 34 class III drugs (38%) and 8 are class IV drugs (9%). Considering from the Lindenberg's research, all drugs could not belong to one of the four classes, and sometimes they are categorized provisionally or indecisively. The following drugs are still controversial in determining their class because of lack of solubility and permeability data: albendazole, amitriptyline, atropine sulfate, chlorpheniramine, chlorpromazine, ciprofloxacin, clofazimine, clomiphene, clomipramine, dexamethasone, diloxanide, efavirenz, ethinylestradiol, folic acid, glibenclamide, glyceryl trinitrate, haloperidol, isosorbid dinitrate, ivermectin, lamivudin, levamisole, lopinavir, mebendazole, mefloquine, metoclopramide, morphine sulfate, niclosamide, nystatin, pyrantel, pyrimethanmine, quinine, retinol, senna, sodium iodide, spironolactone, sufadiazine, sulfasalazine, triclabendazole, verapamil, warfarin sodium (Lindenberg et al., 2004).

## New Challenges to Modify the BCS

**Biopharmaceutics drug disposition classification system (BDDCS)**

On the basis of the BCS, Wu and Benet proposed a new modest revision of BCS designed to determine the criteria on drug disposition, namely, biopharmaceutics drug disposition classification system (BDDCS) (Wu et al., 2005). They demonstrated that the BCS is useful in predicting the predominant routes of elimination, efflux effects, absorptive transporters on oral absorption, and that this newly revised system might guarantee the predictability of *in vivo* disposition for all four classes, as well as increasing the number of Class I drugs eligible for bioequivalence study waivers (Table II).

In this article, the authors suggested that drugs which belong to the same class on the BCS have similar tendency toward drug elimination and disposition: the elimination of class I and II drugs are mainly due to metabolism, while class III and IV drugs mainly undergo renal and/or biliary elimination of unchanged forms. Moreover, they also proposed that the classified drugs have their own tendency toward transporter effect on drug disposition. In the case of class I drugs, their transporter effects are considered to be negligible, and class II and III drugs appear to have predominant efflux and absorptive transporter effects, respectively. In addition, class IV drugs are significantly influenced by both absorptive and efflux transporter effective. The authors finally proposed the new concept of namely, BDDCS, which classifies drug into four categories depending on the main two determining factors of drug solubility and metabolism extent (Wu et al., 2005). Thus, drugs belong to four different classes: class I (high solubility and extensive metabolism), class II (high solubility and poor

**Table II.** *Disposition Characteristics of Drugs Categorized by theBbiopharmaceutics Classification System*

| Class | Solubility | Permeability | Elimination routes | Effect of transporter on disposition |
|---|---|---|---|---|
| I | High | High | Metabolism | Minimum transporter |
| II | Low | High | | Predominant efflux transporter |
| III | High | Low | Renal and/or biliary excretion | Predominant absorptive transporter |
| IV | Low | Low | | Both efflux and absorptive effect |

Adapted and reorganized from the figure 2 and 3 in the literature of Wu et al., 2005

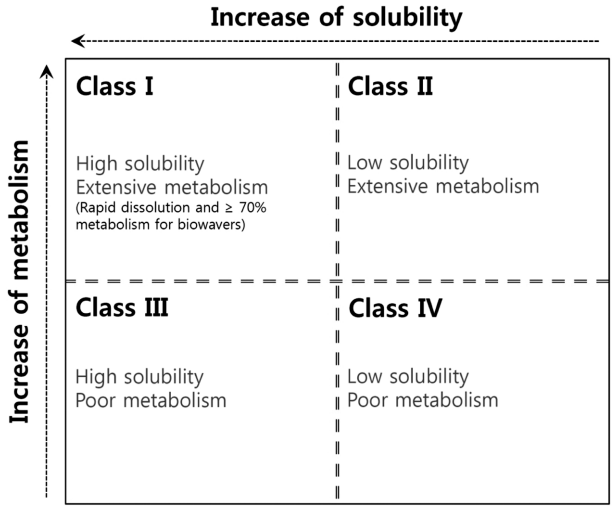


**Figure 2.** The biopharmaceutics drug disposition classification system (BDDCS) suggested by Wu et al. (Reorganized by the figure 6 in the literature Wu et al., 2005).

metabolism), class III (low solubility and extensive metabolism), and class IV (low solubility and poor metabolism) (Figure 2).

**Classification system using intrinsic dissolution rate (IDR)**

The intrinsic dissolution rate (IDR), which usually uses a compressed disk, has been an advanced alternative to characterize solid drug substances for many years (Amidon et al., 1982; Yu et al., 2004). Saying an example, it could be used to understand the relationship or correlation between the dissolution rate and the crystalline form and also to study the effects of surfactants and pH on the solubilization of poorly soluble drugs (Jinno et al., 2000; Dahaln et al., 1987). In a general definition, IDR is considered as the dissolution rate of a pure drug substance under the condition of constant surface area, agitation or stirring speed, pH and ionic strength of the dissolution medium (Yu et al., 2004). Intrinsic dissolution is a rate phenomenon instead of an equilibrium phenomenon, and it might correlate more closely with *in vivo* drug dissolution than solubility. Therefore, it may be preferred as the rate of mass transfer from the solid surface to the liquid phase.

Yu et al. suggested detailed conditions and protocols for the robust and reproducible IDR study in an attempt to modify the BCS, and concluded that the variables in the production of the drug disk, for example compression pressure, dissolution medium volume, and die position, did not give significant effect on IDR. Especially, they proposed four different values that may influence the result of IDR: a compression force of 2000 psi, unless the disk fragments in solution in which case a lower force needs to be employed. Dissolution medium volume is the standard 900 mL unless higher concentrations are needed for low solubility drugs where 225 mL can be used. The die position and rotational speed are 0.5 in. and 100 rpm, respectively (Yu et al., 2004. In this way, the authors concluded that IDR generally correlated with the BCS solubility classification with 0.1 mg/min/cm$^2$ as a class boundary unless the dose is either extremely low or high where a discrepancy may exist between the solubility and DIDR methods.

**Classification system using animal permeability data**

Thus far, there is no systemic research to investigate the individual permeability of a wide variety of drugs in human subjects because it is extremely limited to perform this kind of study *in vivo* or *in situ* conditions. Therefore, an alternative approach using rat intestinal permeability has been done. It is very obvious that this trial is not an advanced experimental method, but if the permeabilities of drug in rat intestine correlate well with those in human, this may predict the classification of drug candidates without considerable cost in the human clinical phase (Yu et al., 2004). Zakeri-Milani suggested the final method combined with intrinsic dissolution rate (IDR), and concluded that this alternative approach using rat intestinal permeability have great reliability with quite good correlation with human data (Zakeri-Milani et al., 2009a,b,c). They categorized drugs into four classes with the detailed specification for according to the rat intestine permeability and IDR as follows:

Class 1: $P_{eff,rat}$ (cm/s) > $5 \times 10^{-5}$ or $P_{eff,human} > 4.7 \times 10^{-5}$, IDR (mg/min/cm$^2$) > 2. Propranolol, metoprolol, veraparmil and antipyrin belong to this class.

Class 2: $P_{eff,rat} > 5 \times 10^{-5}$ or $P_{eff,human} > 4.7 \times 10^{-5}$, IDR < 1. Ketoprofen, naproxen, piroxicam, ibuprofen and carbamazepine belong to this class.

Class 3: $P_{eff,rat} < 5 \times 10^{-5}$ or $P_{eff,human} < 4.7 \times 10^{-5}$, IDR > 2. Atenolol, ranitidine and cimetidine belong to this class.

Class 4: $P_{eff,rat} < 5 \times 10^{-5}$ or $P_{eff,human} < 4.7 \times 10^{-5}$, IDR < 1. Furosemide belongs to this class.

**BCS specialized for new molecular entities and marketed drugs**

Papadopoulou et al. tried to develop different two approaches for the biopharmaceutics classification for new molecular entities (NMEs) and marketed drugs (MDs), respectively. They insisted that two rates related with permeation and dissolution are major determinants for oral absorption, but that such values change continuously over time and thus are impractical to the use of biopharmaceutical classification purpose (Papadopoulou et al., 2008). They theoretically reconsidered the kinetics of permeation and dissolution in terms of the relationships between the solubility/dose ratio and the fractions of dose dissolved and absorbed (Papadopoulou et al., 2008). They used two important values for analyzing in respect to the physiological mean intestinal transit time (MITT) to identify a meaningful cutoff point for drug dissolution and permeation. Also, they suggested two terms of mean time calculations for drug dissolution (MDT) and GI wall permeation (MPT). In this article, a physiologically based cutoff time point for dissolution and permeation was used to differentiate rapidly from slowly dissolving-permeating marketed drugs, which were classified into four classes of BCS-MD using their dissolution index (DI = MITT/MDT) and permeation index (PI = MITT/MPT) values as follows: Class I (DI ≥ 3, PI ≥ 3), class II (DI < 3, PI ≥ 3), class III (DI ≥ 3, PI < 3) and class IV (DI < 3, PI < 3).

## Conclusion

Since the introduction of biopharmaceutics classification system (BCS), it has contributed to categorizing drugs according to the criteria of physicochemical characteristics. It has also played pivotal role in decreasing the regulatory burden by allowing a waiver of *in vivo* bioequivalence studies for many drugs, especially class I. However, more careful attention on data collection and research design should be paid to other classes (II, III, and IV) because little predictive case has been made for such classes. Recently, dissolution profiles using intrinsic dissolution rate are considered to be more reliable than solubility, but more scientific research data should be also collected and analyzed for this purpose. Finally, a new trial of biopharmaceutics drug disposition classification system (BDDCS) shows limited application to the BA and BE studies, but if properly modified and approved by the FDA, this kind of approach would be a valuable prediction tool on the pharmacokinetic and biopharmaceutical behaviors of many drugs in terms of solubility and metabolism, in near future.

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