The Impact of Formulation on Bioavailability: Summary of Workshop Discussion

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Overview

Bioavailability and bioequivalence of drug products play a critical role in drug development, regulatory review/approval and in clinical use of drug products. The regulatory requirements for bioavailability and bioequivalence were established ~20 y ago in response to numerous reports of therapeutic failures that were linked to formulation differences.

Formulation factors that affect bioavailability and bioequivalence may be broadly classified into two categories.

1. Factors that affect drug dissolution or release from the dosage form: drug dissolution or release is considered as a prerequisite to the drug absorption process. Therefore, compendial dissolution test methods were introduced to replace, for most solid dosage forms, disintegration testing.

2. Factors related to excipients or inactive ingredients that may affect drug stability (at the site of administration) and drug absorption and or metabolic processes.

In U.S. statute, bioavailability is defined as "the rate and extent to which the active ingredient or active moiety is absorbed from a drug product and becomes available at the site of action" (Federal Food, Drug and Cosmetic Act, section 505, j, 7). To deliver many drugs to their site(s) of action, we rely on the systemic blood circulation, as opposed to locally acting drug products, such as ointments intended to treat a skin condition. For drug products intended for systemic absorption, bioavailability (from an extravascular site of administration) of a drug from its dosage form is generally determined by comparing its pharmacokinetic profile in blood with that after intravascular (e.g., intravenous) administration of the same drug in solution.

When it is not feasible to quantify drug levels in blood or other relevant biological fluids and for products intended for local delivery or action (e.g., ointments for skin application) other approaches have been developed. These include comparative clinical trials, pharmacodynamic studies and in vitro studies. Under certain circumstances, Food and Drug Administration (FDA) regulations allow use of in vitro studies for documentation of bioavailability/bioequivalence, where a suitable in vitro/in vivo correlation may be established.

Bioequivalence is the comparative evaluation of drug bioavailability from two different formulations or products that contain the same drug. Bioequivalence is defined in the United States as "the absence of a significant difference in the rate and extent to which the active ingredient or active moiety in pharmaceutical equivalents or pharmaceutical alternatives becomes available at the site of drug action when administered at the same molar dose under similar conditions in an appropriately designed study" (Federal Food, Drug and Cosmetic Act, section 505, j, 7). Drug products are considered pharmaceutical equivalents if they contain the same active ingredient(s), are of the same dosage form, route of administration and are identical in strength or concentration. Drug products are considered pharmaceutical alternatives if they contain the same therapeutic moiety but are different salts, esters or complexes of that moiety or are different dosage forms or strengths (Approved Drug Products with Therapeutic Equivalence Evaluations, FDA, Center for Drug Evaluation and Research, February 2000).

The FDA classifies therapeutically equivalent as those products that meet the following general criteria: 1) they are approved as safe and effective; 2) they are pharmaceutical equivalents in that they contain identical amounts of the same active drug ingredient in the same dosage form and route of administration and meet compendial or other applicable standards of strength, quality, purity and identity; 3) they are bioequivalent in that they do not present a known or potential bioequivalence problem and they meet an acceptable in vitro standard, or if they do present such a known or potential

1 Summary of workshop discussion held at the conference "Bioavailability of Nutrients and Other Bioactive Components from Dietary Supplements" January 5-6, 2000 in Bethesda, Maryland. This conference was sponsored by the Office of Dietary Supplements, National Institutes of Health and the Life Science Research Office, American Society for Nutritional Sciences. Conference proceedings are published as a supplement to The Journal of Nutrition. Guest editors for the supplement publications were Mary Frances Picciano, Pennsylvania State University, University Park, PA and Daniel J. Raiten, National Institute of Child Health and Human Development, National Institutes of Health, Bethesda, MD.

3 Abbreviation: FDA, Food and Drug Administration.
problem, they are shown to meet an appropriate bioequivalence standard; 4) they are adequately labeled; and 5) they are manufactured in compliance with current good manufacturing practice regulations (Federal Food, Drug and Cosmetic Act, section 505, j, 7).

Although the formulation factors that influence bioavailability and bioequivalence are well established for traditional pharmaceutical products, much work needs to be done for nutrients and botanicals. Although the drug model described above may be appropriate for some botanicals and nutrients, it will not always be applicable. To truly understand how formulation factors affect bioavailability will require many years of study. Presented below are what, in the Working Group’s collective opinion, should be the initial steps in understanding bioavailability and bioequivalence of nutrients and botanical products. The ultimate goal of this research should lead to better public health by ensuring that products on the market are bioavailable.

Research priorities

The consensus of the Working Group was that research on bioavailability should have the following priorities.

- Improved public health through a better understanding of safety issues
- Generation of data that would enable consumers and healthcare professionals to make better educated decisions and choices
- Increased product performance creation of novel delivery systems
- Identification of critical formulation variables
- Identification of sources of variability due to formulation factors
- Improved consistency for supplements used in different clinical trials
- Development of general research models and standardized methods for formulation development
- Definition of quality standards

The discussants also emphasized the importance of in vitro testing, clinical trials, research projects that address significant health concerns and projects using systems with the greatest market prevalence.

Research recommendations

To address these themes and achieve the above objectives, the Working Group identified the following research priorities presented with brief justifications.

- Classification of nutrients and botanicals in general categories
  - Because of the diversity of nutrients and botanicals, different approaches are needed to study different types of compounds. Therefore, a classification system is needed to categorize nutrients and botanicals; the system could be based upon their physical and chemical properties and biological disposition characteristics. This classification scheme should group compounds with similar properties such that similar formulation principles and test protocols can be applied to the group.
  - The discussants concluded that the biopharmaceutical classification system used for drugs would be a good archetype for a nutrient and botanical classification scheme (Amidon et al., 1995). The Working Group urged that all subsequent items on the research agenda be considered in the context of this classifications system.
  - For example, one set of study or test protocols and analytical techniques can be used for minerals, oil-soluble vitamins or water-soluble vitamins. Another example, similar test methods can be used for botanical extracts, although different methods may be used for botanical prepared by grinding various plant parts, i.e., without extraction. Compounds with different biological disposition characteristic, like endogenous nutrients, may have to be studied differently from botanicals that do not have an endogenous presence.

- Different types of dosage forms such as controlled release or immediate release may also need to be classified differently due to differences in the way the delivery system presents a compound to the body. For example, if a nutrient has a saturable active transport system, then the absorption would be dose-dependent and, hence, bioavailability could be affected. The bioavailability of this nutrient could be different when absorbed from food (i.e., low dose) versus a megadose vitamin. If the nutrient’s active transport system is localized to a region of the gastrointestinal tract, then a controlled release delivery system could miss the window of absorption and, hence, alter bioavailability.

- Development of standard definitions for bioavailability for each class of compounds
  - For botanical products a traditional definition based upon a drug model is probably adequate. However, for some vitamins and minerals, a definition based upon a drug model may not work because of the endogenous presence of these compounds. In addition, nutrients are subject to the body’s homeostatic mechanisms that can alter the equilibrium between plasma and the site of action/utilization, which is an inherit assumption in the traditional drug model of bioavailability.

Identification of critical formulation variables

For drugs, the mechanisms by which a formulation affects bioavailability have been extensively studied and most of the important factors have been documented in the literature and are part of FDA’s regulatory policies. The bioavailability and absorption of nutrients from food have also been extensively studied. However, nutrients are often absorbed differently from drugs and nutritional supplements have a different release profile from food. Thus, the formulation factors known to affect the bioavailability of drugs may not apply to nutrients and the factors known to affect nutrient absorption from food may not apply to supplements. Presently, much more research is needed to identify the critical formulation factors that affect bioavailability and formulation stability for nutritional supplements and the factors that affect the bioavailability and stability of botanical products are largely unknown.

This lack of knowledge makes efficacious supplement formulation almost impossible because formulators do not know which variables are important. Even basic questions, such as, “What should the dosage form do?”, “What is a quality product?”, etc., are not known. Therefore, for a given class of compounds, the critical process and formulation variables that significantly impact bioavailability and product stability must be determined. The goal of this research should be to develop general quantitative strategies and/or methods needed to formulate and produce optimal nutritional supplements and botanical products that are stable.

- Elucidation of mechanisms of interaction
  - A recurring theme at the conference was the interaction between nutrients, botanicals, drugs, usage patterns, dose, diet, biological systems, pathophysiological changes, demographic factors, etc. Studies performed to determine the critical formulation variables described above are typically done with healthy volunteers under standardized conditions. To extrapolate these results to a wider population, the mechanisms by
which a formulation interacts with these different factors to alter bioavailability must be further studied. To determine these mechanisms of interaction, fundamental quantitative studies of the chemical, physical and biological interactions must be conducted. It was believed that these interactions could best be understood by determining the fundamental mechanisms of release, absorption, distribution and utilization of botanical and nutrients. In addition, the physical and chemical factors that adversely affect product stability must be examined. Determination of physical chemical and biological incompatibilities also would be useful.

- In vitro methods for assessing dissolution and absorption.

The Working Group expressed some reservations about the reliance on clinical trials for the study of bioavailability. Although recognizing that clinical trials are the definitive test, the Working Group also noted that they are also the most expensive and time consuming. Therefore, the Working Group urged the development and standardization of in vitro methods as a way to greatly accelerate research. Methods like U.S. Pharmacopeia dissolution and Caco-2, etc. can be done faster and cheaper than can a clinical trial. In addition to being faster and cheaper, in vitro tests can be invaluable when trying to understand formulation effects on bioavailability. With clinical data, there is always a higher variability associated with the results, which makes assessing subtle formulation effects and interactions impossible without corresponding in vitro data. For product quality assurance testing, standardized in vitro methods are necessary for clinical studies in which the validity of the results depends upon each patient receiving the same treatment.

For the in vitro data to have the greatest utility, the in vitro/in vivo correlation must be established for each test method. This is particularly true for minerals, like Ca, where there is a poor correlation between solubility and bioavailability. In the pharmaceutical literature, there are many methods available for the determination of the in vitro/in vivo correlation. It is recommended that these be used as a prototype for these studies (Eddington et al. 1998, Polli 1998).

- Product comparison and bioequivalence and bioavailability.

When assessing dietary intake, one needs to determine how much is absorbed (i.e., bioavailability) and to make comparisons among different nutrient sources. To make these determinations, general research methodologies must be developed to enable the systematic study of bioavailability and bioequivalence of nutrient and botanical supplements.

Among the many important issues regarding bioavailability and bioequivalence, the Working Group focused on the following as meriting particular attention: How does absorption of a nutrient from food compare with absorption from a supplement? For example, how much folic acid is absorbed from a glass of fortified orange juice versus a prenatal multivitamin supplement? Are natural sources better than synthetic sources? Is one salt form more bioavailable than another? For example, with Ca supplements: Is one salt type better than another? Are there physical differences such as particle size that affect bioavailability? and for botanicals: How different is the bioavailability of an extract from the bioavailability of a ground plant?

This information would be very valuable to consumers and clinicians who need to purchase or prescribe different products from different sources. However, for these data to be useful, the methods of measurement and comparison must be standardized. In addition, clinical studies must be conducted with a sufficient sample size such that statistically significant results can be derived from the study. Toward this end, the Working Group strongly urged that any studies funded have sufficiently large sample sizes to ensure that statistically significant results can be obtained from the study. The standardized statistical methods for determining bioavailability and bioequivalence of botanicals are well established in pharmaceutical research and would be a good place to start for the study of nutrients and botanicals.

An essential issue in the expansion of our knowledge about bioavailability and bioequivalence of botanicals is how dose, potency, bioavailability, etc., should be determined numerically. To determine the bioavailability and bioequivalence of botanicals requires quantification of dose and concentration in biological fluids. However, with most botanicals, there are a large number of possible bioactive components that may act singly or together, which makes explicit quantification of active ingredient(s) impossible.

One way of dealing with this problem is the use of marker compounds. Marker compounds are characteristic compounds that may be associated with the therapeutic activity of the botanical; these marker compounds are used as surrogates for the active compound. Using this approach, the marker compound is quantified and calculations are based upon this compound or group of compounds. For example, if one wanted to do a study of St. John's Wort (Hypericum perforatum), the typical marker compounds used are hypericin and pseudohypericin. However, the drawback is that if chosen incorrectly, activity may not be associated with the marker compound.

Within the Working Group, the use of marker compounds was controversial. Consequently, the Working Group endorsed an expanded research effort to determine whether the use of marker compounds is the best way to assess the bioavailability of botanical products and if not, to determine the most viable alternative method. In addition to the conceptual issue, the Working Group recommended efforts to identify an acceptable process by which marker compounds might be chosen. For example, should the most hydrophilic hydrophobic marker compound be chosen? How would the type of formulation affect the choice of marker compounds?

- Modulation of bioavailability

Given all the recent innovations developed for the modulation of bioavailability of drug products, the Working Group recommended the adaptation of these methods to the study of botanical supplements. For certain cases, they could be used to improve product quality.

- Optimal product use

In addition, information should be gathered for the optimal use of nutritional and botanical products. For example, is time of administration important? Should the product be taken with or without food? This information would be valuable for supporting label claims.

- Analytical methods

Although not the purview of this Working Group, it was generally agreed that research leading to better analytical methods would greatly facilitate this research agenda.

LITERATURE CITED

