

BIOAVAILABILITY AND BIOEQUIVALENCE IN DRUG DEVELOPMENT: CURRENT INSIGHTS AND FUTURE PERSPECTIVES

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ABSTRACT

Bioavailability and bioequivalence are pivotal concepts in pharmaceutical research, playing a crucial role in ensuring the safety, efficacy, and interchangeability of drug products. This paper presents a comprehensive review of the current insights and future perspectives surrounding bioavailability and bioequivalence in the context of drug development. The introduction provides a foundational understanding of these concepts, elucidating the significance of bioavailability as a determinant of drug action and the critical role of bioequivalence in evaluating generic drug products. Factors influencing bioavailability, encompassing physiological, formulation-related, and administration route variations, are thoroughly examined. The methods employed to assess bioavailability, both in vitro and in vivo, are explored, with a focus on key pharmacokinetic parameters. Advancements in biopharmaceutical modeling, simulation, and biorelevant dissolution testing are presented as emerging trends with the potential to refine bioavailability predictions. The incorporation of physiologically-based pharmacokinetic modeling is showcased as a promising approach to enhance bioavailability estimation. This review paper encapsulates the current state of knowledge regarding bioavailability and bioequivalence in drug development. It emphasizes the dynamic nature of these concepts, highlighting the ever-evolving methodologies, regulations, and technologies that shape their application. The insights presented herein provide a foundation for researchers, clinicians, regulators, and industry stakeholders to navigate the intricate landscape of bioavailability and bioequivalence, driving the field toward safer, more effective, and innovative drug development practices in the future.

KEYWORDS: Bioavailability, Bioequivalence, Drug development, Pharmacokinetics, Generic drugs, Regulatory guidelines, Biopharmaceutical modeling.

INTRODUCTION

In the realm of modern pharmaceutical science, the development and evaluation of drug products are governed by the principles of bioavailability and bioequivalence. These concepts are fundamental to ensuring that medications are not only safe and effective but also interchangeable and reliable in their therapeutic outcomes. The understanding and application of bioavailability and bioequivalence have revolutionized drug development processes, enabling researchers, clinicians, and regulatory authorities to make informed decisions that impact patient care and public health.^[1,2,3]

Bioavailability refers to the fraction of an administered drug that reaches the systemic circulation and is available to exert its intended pharmacological effect. In essence, it determines the extent and rate at which a drug is absorbed from its dosage form and becomes available at the target site of action. Bioavailability is influenced by a multitude of factors, including the physicochemical properties of the drug, the formulation used, and the route of administration. Understanding bioavailability is

crucial for optimizing drug formulations and dosing regimens, as variations in absorption can result in differences in therapeutic response. Bioequivalence, on the other hand, addresses the interchangeable nature of drug products. It is the demonstration that two pharmaceutical formulations containing the same active ingredient(s) are pharmaceutically equivalent and produce similar concentrations in the bloodstream when administered in equivalent doses. This concept is particularly relevant in the context of generic drugs, where manufacturers seek to produce cost-effective alternatives to brand-name medications. Demonstrating bioequivalence is a regulatory requirement to ensure that generic products are therapeutically equivalent to their reference counterparts, thus allowing patients and healthcare providers to confidently switch between different versions of the same medication.^[1,2]

In this comprehensive review, we delve into the intricacies of bioavailability and bioequivalence in drug development. We explore the factors that influence the availability of drugs in the body, ranging from

physiological variations among individuals to the specific formulation technologies employed. We dissect the methodologies and techniques used to assess bioavailability, including both in vitro experiments and in vivo studies that track drug concentrations over time. Moreover, we shed light on the critical role of pharmacokinetic parameters such as peak concentration (C_{max}), area under the concentration-time curve (AUC), and time to reach maximum concentration (T_{max}) in evaluating drug performance.

Furthermore, this review navigates the regulatory landscape governing bioequivalence, elucidating the stringent guidelines set by regulatory agencies like the U.S. Food and Drug Administration (FDA) and the European Medicines Agency (EMA). We explore the challenges posed by drugs with narrow therapeutic indices, where slight deviations in bioequivalence could have substantial clinical implications. As the field advances, so do the tools and strategies for predicting and enhancing bioavailability. Biopharmaceutical modeling and simulation techniques offer insights into how drug formulations interact with the body, aiding in the design of optimal drug delivery systems. The integration of physiologically-based pharmacokinetic modeling takes us closer to predicting drug behavior in diverse patient populations, guiding personalized treatment approaches.

Factors influencing bioavailability

Bioavailability, a critical parameter in drug development, is subject to a myriad of factors that collectively determine the extent and rate of drug absorption, distribution, metabolism, and excretion. These factors, ranging from physiological variations to formulation characteristics, intricately shape the pharmacokinetic profile of a drug and consequently influence its therapeutic efficacy. Understanding these factors is essential for optimizing drug formulations, dosing regimens, and clinical outcomes. In this section, we delve into the multifaceted aspects that impact bioavailability.^[3]

1. Physiological variations

Gastrointestinal (GI) Conditions: Gastrointestinal disorders, such as gastroenteritis and inflammatory bowel diseases, can alter the absorption rate and extent of drugs due to changes in GI motility and permeability.

Age: Neonates, infants, and the elderly often exhibit altered gastrointestinal transit times and reduced enzymatic activity, impacting drug absorption and metabolism.

Gender: Hormonal differences between genders can influence drug distribution and metabolism, leading to variations in bioavailability.

Genetics: Genetic polymorphisms can affect drug metabolizing enzymes, transporters, and receptors, leading to inter-individual variability in drug response.

2. Formulation and Dosage form

Dosage form: Different formulations (tablets, capsules, injections, etc.) can result in varying rates of dissolution and disintegration, affecting drug absorption.

Excipients: Inactive ingredients in formulations can influence drug solubility, stability, and release, impacting bioavailability.

Particle size: Smaller particle sizes can increase surface area, enhancing dissolution and absorption rates.

pH Sensitivity: Some drugs are formulated as pH-sensitive formulations, which can influence drug dissolution and absorption depending on the gastrointestinal pH.

3. Route of administration

Oral administration: Oral drugs pass through the gastrointestinal tract, where factors like pH, food interactions, and enzymatic activity influence drug solubility and absorption.

Intravenous administration: Intravenously administered drugs bypass absorption barriers, resulting in complete bioavailability, but distribution and elimination processes still impact overall drug exposure.

Topical and Transdermal routes: Skin permeability, blood flow, and the presence of barriers like stratum corneum influence drug absorption through topical and transdermal routes.

4. Food and Drug interactions

Food Effects: Food can delay or enhance drug absorption due to interactions with enzymes and alterations in gastric emptying and intestinal motility.

Drug-Drug Interactions: Concurrent administration of drugs can influence drug metabolism and transport, impacting overall bioavailability.

5. First-Pass metabolism

Liver metabolism: Drugs absorbed from the GI tract first pass through the liver before reaching systemic circulation. Hepatic metabolism can significantly reduce bioavailability by metabolizing drugs into inactive or less active metabolites.

6. Disease states

Liver and Kidney dysfunction: Impaired liver or kidney function can disrupt drug metabolism and elimination, leading to altered bioavailability.

Circulatory disorders: Poor blood circulation can affect drug distribution to target tissues, influencing bioavailability.^[4,5,6]

Methods for assessing bioavailability

Accurately assessing bioavailability is essential for understanding how drugs are absorbed, distributed, metabolized, and eliminated in the body. To achieve this, researchers employ a combination of in vitro and in vivo methods, along with various analytical techniques. These methodologies provide insights into pharmacokinetic parameters that characterize a drug's behavior, such as peak concentration (C_{max}), area under the

concentration-time curve (AUC), and time to reach maximum concentration (T_{max}). This section elucidates the approaches and techniques used in assessing bioavailability.

In vitro methods

In vitro methods offer controlled settings for investigating drug behavior outside the complex environment of the human body. Dissolution testing, a cornerstone of in vitro assessment, involves simulating the drug's release from its dosage form under standardized conditions. By mimicking the gastrointestinal environment, dissolution testing provides insights into how formulations disintegrate and release their active compounds. Complementary to dissolution testing, permeability assays employing cell-based models, such as Caco-2 and MDCK cell lines, allow researchers to gauge how readily a drug crosses intestinal barriers. These assays offer predictive information about a drug's absorption potential and its ability to traverse biological membranes.

In vivo methods

Moving beyond controlled environments, in vivo methods directly involve the administration of drugs to living organisms. Pharmacokinetic studies stand at the core of these approaches, encompassing the measurement of drug concentrations in bodily fluids over time. By tracing the concentration-time profiles, pharmacokinetic parameters like C_{max} (the peak concentration achieved), AUC (the area under the concentration-time curve, reflecting overall exposure), and T_{max} (the time taken to reach C_{max}) are derived. These parameters collectively characterize a drug's absorption, distribution, metabolism, and elimination kinetics. Bioavailability studies, a subset of in vivo methods, compare the performance of a test formulation to a reference formulation. These studies help ascertain the extent and rate of drug absorption, providing essential insights for formulation optimization.

Pharmacokinetic parameters

Pharmacokinetic parameters distill intricate concentration-time profiles into quantifiable values that hold critical therapeutic implications. C_{max}, for instance, provides information about the peak concentration achieved in the bloodstream post-administration. This parameter indicates how quickly the drug reaches its maximum concentration, which is pivotal for drugs requiring rapid onset of action. The AUC reflects the cumulative exposure of the body to the drug over time, offering insights into the overall therapeutic effect and potential toxicity. T_{max} adds another layer of understanding, indicating the time taken for the drug to reach C_{max}. This parameter influences the drug's clinical response time and informs dosing schedules.^[4,5]

Analytical techniques

Analytical techniques play an indispensable role in quantifying drug concentrations in biological samples.

High-Performance Liquid Chromatography (HPLC), a mainstay in pharmaceutical analysis, employs chromatographic separation to identify and quantify drug compounds. Gas Chromatography (GC), often coupled with mass spectrometry, specializes in volatile and thermally stable compounds. Liquid Chromatography-Mass Spectrometry (LC-MS) combines separation with mass analysis, offering high sensitivity and specificity. Immunoassays like Radioimmunoassay (RIA) and Enzyme-Linked Immunosorbent Assay (ELISA) utilize antigen-antibody interactions to quantify drugs or metabolites. Advanced techniques like nuclear imaging (PET, SPECT) provide real-time visualization of drug distribution in living subjects.

In essence, these methods and techniques form a tapestry of insights that unravel the complex journey of a drug within the human body. They serve as invaluable tools for researchers, clinicians, and regulatory bodies, enabling informed decision-making at every stage of drug development. The subsequent sections will navigate the realm of bioequivalence, shedding light on its significance and the regulatory guidelines that govern this crucial aspect of drug evaluation.^[6,7]

Significance of bioequivalence

Bioequivalence studies play a pivotal role in the approval process of generic drugs, ensuring that they are therapeutically equivalent to their brand-name counterparts. Generic drugs are cost-effective alternatives to branded medications, providing patients with access to affordable treatments. However, to be approved, generic drugs must demonstrate bioequivalence to the reference (innovator) drug. This ensures that generic versions deliver the same active ingredient in the body at a similar rate and extent, thus yielding identical clinical effects.

The significance of bioequivalence studies lies in their ability to provide assurance to regulatory agencies, healthcare providers, and patients that generic drugs perform in a manner equivalent to the established reference product. These studies are not only a regulatory requirement but also a means to guarantee patient safety and therapeutic efficacy, facilitating the interchangeability of generic drugs with their branded counterparts.

Regulatory guidelines for demonstrating bioequivalence

Regulatory agencies, such as the U.S. Food and Drug Administration (FDA) and the European Medicines Agency (EMA), provide comprehensive guidelines outlining the rigorous standards that generic drugs must meet to establish bioequivalence. These guidelines dictate the design and conduct of bioequivalence studies, ensuring robustness, reliability, and comparability of results.

Bioequivalence studies typically follow a randomized, crossover design, where healthy subjects receive both the generic and reference products. Key pharmacokinetic parameters, including C_{max}, AUC, and T_{max}, are compared statistically to assess whether the generic product falls within a predefined acceptable range in comparison to the reference product. These guidelines also address factors such as subject selection, washout periods, and analytical methods for quantifying drug concentrations.^[7,8,9]

Challenges in establishing bioequivalence, Including narrow therapeutic index drugs

While bioequivalence studies are crucial, challenges can arise, especially when dealing with drugs with a narrow therapeutic index (NTI). NTI drugs have a small margin between therapeutic and toxic doses, making small variations in bioavailability potentially significant. Achieving bioequivalence for NTI drugs demands heightened precision due to the critical nature of their dosing.

For NTI drugs, the acceptable range of bioequivalence may be narrower, increasing the difficulty of meeting regulatory criteria. Additionally, the inherent variability of both the drug and human responses further complicates bioequivalence assessment. The sensitivity to changes in formulation, manufacturing processes, and even minor physiological differences can pose challenges in demonstrating equivalence.^[8]

Regulatory landscape

The regulatory landscape governing bioavailability and bioequivalence studies is a cornerstone of drug development and approval. Regulatory agencies across the globe establish guidelines and standards to ensure that pharmaceutical products meet stringent criteria for safety, efficacy, and interchangeability. These regulations provide a framework that governs how drugs are evaluated, tested, and approved based on their bioavailability and bioequivalence profiles.

Role of regulatory agencies

Regulatory agencies such as the U.S. Food and Drug Administration (FDA), the European Medicines Agency (EMA), Health Canada, and similar bodies worldwide play a critical role in setting and enforcing standards related to bioavailability and bioequivalence. These agencies aim to strike a balance between facilitating access to safe and effective drugs and maintaining high-quality standards within the pharmaceutical industry.

Bioavailability and Bioequivalence guidelines

Regulatory agencies publish comprehensive guidelines outlining the requirements for conducting bioavailability and bioequivalence studies. These guidelines encompass study designs, methodologies, statistical analyses, and acceptable limits for key pharmacokinetic parameters. They provide a blueprint for demonstrating the

therapeutic equivalence of generic drugs to their reference products.

Regulatory submissions

Pharmaceutical companies seeking approval for generic drugs are required to submit a wealth of data, including the results of bioavailability and bioequivalence studies, as part of their regulatory submissions. These submissions should demonstrate that the generic drug meets the predefined bioequivalence criteria and is therefore suitable for approval.

Generic drug approval process

The approval process for generic drugs involves a thorough review of the submitted data by regulatory agencies. If the bioavailability and bioequivalence data align with the established criteria, the generic drug is deemed interchangeable with the reference product. This approval allows patients and healthcare providers to confidently switch between the generic and reference drugs.^[7,8,9]

International harmonization

Efforts have been made to harmonize regulatory standards across different countries to streamline drug development and approval. Initiatives like the International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use (ICH) aim to establish common guidelines and practices to ensure that drugs can be developed and approved across various regions with minimal differences.

Ensuring patient Safety and Equivalence

The overarching goal of these regulations is to ensure patient safety and maintain the integrity of the pharmaceutical market. By setting rigorous standards for bioavailability and bioequivalence, regulatory agencies minimize the risk of substandard drugs entering the market and provide patients with access to safe and effective medications.

Bioavailability and Bioequivalence studies design

The intricate process of designing bioavailability and bioequivalence studies is a pivotal aspect of drug development, underpinning the assurance of therapeutic equivalence between generic and reference drug products. These studies are meticulously crafted endeavors that demand thoughtful consideration of various parameters, methodologies, and statistical analyses to yield reliable and meaningful results. By adhering to stringent study designs, researchers can generate data that regulatory agencies rely upon to make informed decisions about the approval and interchangeability of generic drugs.

Comparative study designs lie at the heart of bioavailability and bioequivalence studies, facilitating a head-to-head assessment of the test formulation (generic drug) against the reference formulation (innovator drug). Two prominent study designs are employed to achieve

this: the crossover design and the parallel design. In the crossover design, participants are administered both formulations in a specific sequence, allowing each individual to serve as their own control. The inclusion of washout periods between administrations helps mitigate any potential carryover effects. On the other hand, the parallel design divides participants into two separate groups, each receiving one formulation. This design is particularly advantageous for drugs with extended half-lives, reducing the likelihood of order effects and simplifying the study structure. Key to the success of these studies are the chosen study endpoints. Among these, pharmacokinetic parameters take center stage. Parameters such as C_{max} (peak concentration), AUC (area under the concentration-time curve), and T_{max} (time to reach peak concentration) are of paramount importance. These parameters effectively characterize the drug's absorption, exposure, and onset of action, collectively offering insights into its overall behavior within the body. Consequently, the selection of appropriate endpoints is crucial to ensure the study's capacity to capture meaningful pharmacokinetic data.

Determining the optimal sample size is a critical component of study design, directly impacting the statistical power of the study and its ability to detect clinically relevant differences between the test and reference formulations. Variability in pharmacokinetic parameters within and between subjects plays a pivotal role in sample size determination, alongside the regulatory acceptable range of deviation from the reference product. Achieving an accurate and robust sample size calculation is essential to ensure the study's credibility and reliability. The statistical analysis employed in these studies is equally significant, as it guides the interpretation of the generated data. Two One-Sided Tests (TOST), a widely accepted approach, evaluates whether the differences in C_{max} and AUC fall within a predefined acceptable range, effectively demonstrating bioequivalence. Another essential tool is the establishment of a 90% confidence interval (CI), with a CI lying within the acceptable range indicating bioequivalence. These statistical techniques provide a framework for conclusively assessing the therapeutic equivalence of generic drugs to their reference counterparts.

However, special considerations must be taken into account, particularly for drugs with distinct characteristics. Narrow therapeutic index (NTI) drugs, which possess a small margin between therapeutic and toxic doses, often necessitate narrower acceptance limits to ensure consistency in therapeutic effects. Similarly, drugs characterized by high variability in bioavailability might require adjustments in study design, larger sample sizes, or alternative statistical approaches. Ethical and practical considerations guide the implementation of these study designs. Ethical review boards ensure participant safety, the provision of informed consent, and adherence to ethical guidelines. Balancing the depth of

data collection with participant convenience is essential to design study durations that align with ethical standards and yield accurate pharmacokinetic profiles.^[5,6,7]

Advanced Concepts and Emerging trends

Biopharmaceutical modeling and simulation have revolutionized the field of drug development by providing a predictive framework to understand and optimize drug behavior. These computational techniques leverage physiological and pharmacokinetic data to simulate drug absorption, distribution, metabolism, and excretion *in silico*. This approach offers a comprehensive understanding of how various factors influence bioavailability, aiding in formulation design and dose optimization.

Biopharmaceutical modeling allows researchers to explore different scenarios virtually, assessing the impact of factors such as formulation composition, particle size, and dosage form on drug release and absorption. This predictive capability enhances the efficiency of drug development, enabling the identification of optimal formulations without extensive experimentation. Simulation-based bioavailability predictions guide decision-making processes, reduce costs, and accelerate the path to market for new drugs.^[6,7,8]

Application of biopharmaceutical classification systems

Biopharmaceutical classification systems, such as the Biopharmaceutics Classification System (BCS), classify drugs based on their solubility and permeability characteristics. The BCS categorizes drugs into four classes, offering insights into their potential bioavailability challenges and guiding appropriate development strategies.

Class I drugs are highly soluble and permeable, posing minimal bioavailability concerns. Class II drugs have low solubility but high permeability, often requiring formulation strategies to enhance dissolution. Class III drugs exhibit high solubility but low permeability, necessitating permeation enhancement techniques. Class IV drugs have low solubility and permeability, demanding comprehensive approaches to address both aspects.

These classifications inform decisions on formulation selection, dosage form design, and bioequivalence testing requirements. By aligning development strategies with a drug's biopharmaceutical class, pharmaceutical scientists can streamline drug development, optimize bioavailability, and ensure therapeutic efficacy.^[7,8,9]

Utilization of biorelevant dissolution testing

Biorelevant dissolution testing bridges the gap between *in vitro* dissolution studies and *in vivo* drug behavior. Unlike traditional dissolution testing conducted in simple media, biorelevant dissolution testing mimics the physiological conditions of the gastrointestinal tract,

accounting for factors such as pH, enzymes, and fluid dynamics. This approach provides a more accurate representation of how a drug will dissolve and be absorbed in the body.

Biorelevant dissolution testing is particularly valuable for predicting *in vivo* drug performance and bioavailability. It enables researchers to assess how different formulations interact with the complex gastrointestinal environment, influencing drug release and absorption patterns. By incorporating biorelevant dissolution testing early in the formulation development process, pharmaceutical scientists can identify potential bioavailability challenges, optimize formulations, and tailor drug delivery systems for enhanced performance.

Challenges and Future directions

Narrow Therapeutic Index (NTI) Drugs

NTI drugs, characterized by a minimal difference between therapeutic and toxic doses, present a significant challenge for demonstrating bioequivalence. Meeting stringent regulatory criteria for these drugs can be arduous due to the need for extremely precise formulation and dosing.

Highly variable drugs

Drugs with high intra-subject variability in absorption pose challenges in study design and interpretation. The variability can result from various factors such as genetics, concomitant medications, or even meal effects, making it difficult to ensure consistent bioavailability between formulations.

Biopharmaceutical complexity

The human body is a complex environment where drug absorption is influenced by intricate physiological processes. These complexities can lead to disparities between predicted *in vitro* behavior and actual *in vivo* performance. Capturing these nuances accurately in predictive models remains a challenge.

Generic-Drug specific challenges

Generic drugs might have different excipients, disintegration mechanisms, or release rates compared to the reference product. Formulation variations can affect drug dissolution and, consequently, bioavailability. Standardizing approaches to address these differences is necessary.

Personalized medicine

The future of bioavailability studies could involve personalized medicine approaches. Integrating patient-specific factors like genetics, age, and underlying health conditions could lead to tailored treatment regimens that optimize drug delivery and enhance therapeutic outcomes.

Advanced biopharmaceutical modeling

The ongoing advancement of computational modeling allows for more sophisticated predictions of drug

behavior. These models can simulate drug absorption under various scenarios, enabling formulation optimization and predicting responses in diverse patient populations.

Biologics and Complex drugs

The future of bioavailability research extends beyond traditional small molecules to include complex molecules like biologics. Developing relevant models and methods specific to these intricate drugs is crucial for ensuring accurate predictions of their bioavailability and performance.

In Vitro-In vivo correlations

Enhanced correlations between *in vitro* dissolution data and *in vivo* performance are on the horizon. Improved models will bridge the gap between laboratory studies and clinical outcomes, leading to more accurate predictions of bioavailability and drug response.

Real-time monitoring

Advancements in wearable biosensors and continuous monitoring technologies could revolutionize drug dosing. Real-time monitoring of drug levels in patients would allow for dynamic adjustments of dosing regimens, ensuring optimal bioavailability for each individual.

Regulatory harmonization

The future envisions increased global harmonization of regulatory guidelines. Standardized approaches to bioavailability assessment and approval across regions would simplify the process for drug developers, while maintaining high standards of quality and safety.

Advanced analytical techniques

As analytical techniques continue to evolve, pharmaceutical scientists can expect more efficient and sensitive methods for quantifying drug concentrations. These advancements will provide accurate data for bioavailability studies, enhancing their reliability and predictive power.^[9,10,11]

CONCLUSION

Bioavailability and bioequivalence studies epitomize the synergy between scientific innovation, regulatory diligence, and patient-centric care. They stand as pillars of assurance, offering a profound impact on drug development, patient well-being, and the broader healthcare ecosystem. With every advancement, these studies move us closer to a future where safe, effective, and interchangeable medications are accessible to all, embodying the ultimate promise of pharmaceutical science.

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