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REVIEW ON THE ENHANCEMENT OF THE BIOAVAILABILITY VIA NOVEL DRUG DESIGN SYSTEM

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Abstract :

The clinical effectiveness of therapeutic medicines is largely dependent on oral bioavailability; however, many medications encounter difficulties because of poor solubility, limited permeability, instability, and first-pass metabolism. Prodrug design, molecular modification, lipid-based systems, polymeric and nanocarrier formulations, vesicular carriers, inclusion complexes, and solid-state engineering are some of the methods to get around these restrictions that are examined in this paper. Advanced methods for enhancing absorption, stability, and therapeutic results are also covered, including nanotechnology-based platforms, biopharmaceutical tactics, and intelligent targeted delivery systems. Alongside commercial goods and case studies that show clinical translation, evaluation techniques such as in vitro dissolution, permeability investigations, in vivo pharmacokinetics, and IVIVC are emphasized. The future potential of bioavailability enhancement is indicated by emerging trends including stimuli-responsive systems, multifunctional nanocarriers, and AI-assisted formulation design. These trends highlight the importance of rational drug design in creating safe, efficient, and patient-centered treatments.

Keywords : Bioavailability enhancement, Novel drug delivery systems (NDDS), Lipid-based drug delivery, Polymeric and nanocarrier systems**,** Vesicular drug delivery.

1. Introduction

Because of its affordability, ease of use, and patient compliance, oral medication delivery is still the most used method. However, due to low aqueous solubility, restricted intestinal permeability, chemical or enzymatic instability, and substantial first-pass metabolism, many medicinal medicines have poor oral bioavailability (Vasir & Labhasetwar, 2007; Amidon et al., 1995). Therapeutic efficacy and dosage optimization are directly impacted by bioavailability, which is the percentage of an administered dose that reaches systemic circulation in an active state.

These constraints are frequently not addressed by conventional formulations, which prompts the creation of innovative drug design techniques. To increase solubility, stability, and absorption, strategies such prodrug design, molecular modifications, lipid-based carriers, polymeric nanoparticles, vesicular systems, inclusion complexes, and solid-state engineering have been used (Chawla & Amiji, 2002; Loftsson & Brewster, 2010). Furthermore, precise control over drug release and tissue-specific administration is made possible by targeted delivery systems and advanced nanotechnology, which increases efficacy while reducing systemic side effects (Kreuter, 2001; Petros & DeSimone, 2010).

In order to forecast clinical performance and direct formulation improvement, these methodologies are evaluated using in vitro dissolution, permeability tests, in vivo pharmacokinetics, and in vitro–in vivo correlations (IVIVC) (Shargel et al., 2012; Dressman et al., 2012). The therapeutic importance of these technologies is demonstrated by their conversion into commercial products, such as prodrugs, nanocarriers, and lipid-based formulations. The therapeutic potential of poorly accessible medications may be further expanded by emerging trends including stimuli-responsive systems, multifunctional nanocarriers, and computational-assisted formulation design, opening the door to safer and more successful patient-centric treatments.

The development of bioavailability-enhancing techniques has increased recently due to the integration of high-throughput screening, artificial intelligence (AI), and sophisticated computational tools. Before conducting comprehensive experiments, these methods allow for the quick prediction of solubility, permeability, and stability profiles, which facilitates the logical selection of drug candidates and formulation optimization (Ekins et al., 2019; Zhang et

al., 2021). Furthermore, precise control over drug release kinetics, targeted tissue accumulation, and less systemic toxicity are made possible by the design of multifunctional and stimuli-responsive delivery systems. When taken as a whole, these developments are revolutionizing the field of drug discovery by offering safe, efficient, and patient-centered treatment alternatives that overcome the drawbacks of traditional oral drug administration.

2. Fundamentals of Bioavailability

2.1 Definition and Types

The rate and degree to which an active pharmaceutical ingredient (API) is absorbed from a pharmacological dose form and becomes available in the systemic circulation or at the site of action is known as bioavailability. It is a crucial pharmacokinetic parameter that controls the start, strength, and duration of the therapeutic response. It is especially important for medications taken orally because physicochemical, physiological, and formulation-related factors can affect absorption (Shargel et al., 2012; Dressman et al., 2007).

Types of Bioavailability

- **Absolute bioavailability**

When compared to an intravenous reference formulation that is thought to have 100% bioavailability, it refers to the portion of a given dose that enters the systemic circulation. It illustrates how medication availability is affected by first-pass metabolism and absorption efficiency (Rowland & Tozer, 2011).

- **Relative bioavailability**

Explains how the bioavailability of two medication formulations given via the same route can be compared. It is frequently used to evaluate a test product's performance in comparison to a reference product during formulation development (Shargel et al., 2012).

- **Bioavailability vs. bioequivalence**

While bioequivalence determines if two pharmacological products have similar bioavailability in terms of pharmacokinetic parameters like AUC, C_max, and T_max, bioavailability examines the performance of a single formulation. For generic medication products to be

approved by regulators, bioequivalency must be demonstrated (Chow & Liu, 2008; FDA, 2017).

2.2 Factors Affecting Bioavailability

Bioavailability is determined by a complex interaction of physicochemical, physiological, and formulation-related factors that control the degree and pace of drug absorption. Intrinsic characteristics of poorly soluble compounds, such as aqueous solubility, dissolution rate, particle size, surface area, lipophilicity, ionization (pKa), and solid-state traits like polymorphism and crystallinity, have a significant impact on dissolution and membrane permeation (Yalkowsky & He, 2003; Blagden et al., 2007). These properties frequently direct the choice of approaches to improve solubility, stability, and absorption during drug development. Systemic drug availability is also influenced by physiological variables, such as gastrointestinal pH, gastric emptying, intestinal transit, enzymatic activity, bile salt production, and efflux transporters including P-glycoprotein (Lennernández, 2007). Drug release, stability, and permeability can be modulated concurrently by formulation factors as dosage form design, excipient selection, manufacturing procedures, and drug–excipient interactions, which can either increase or decrease bioavailability (Aulton & Taylor, 2018). Therefore, the logical development of innovative drug delivery methods that maximize bioavailability and therapeutic efficacy requires a thorough understanding of these interrelated factors.

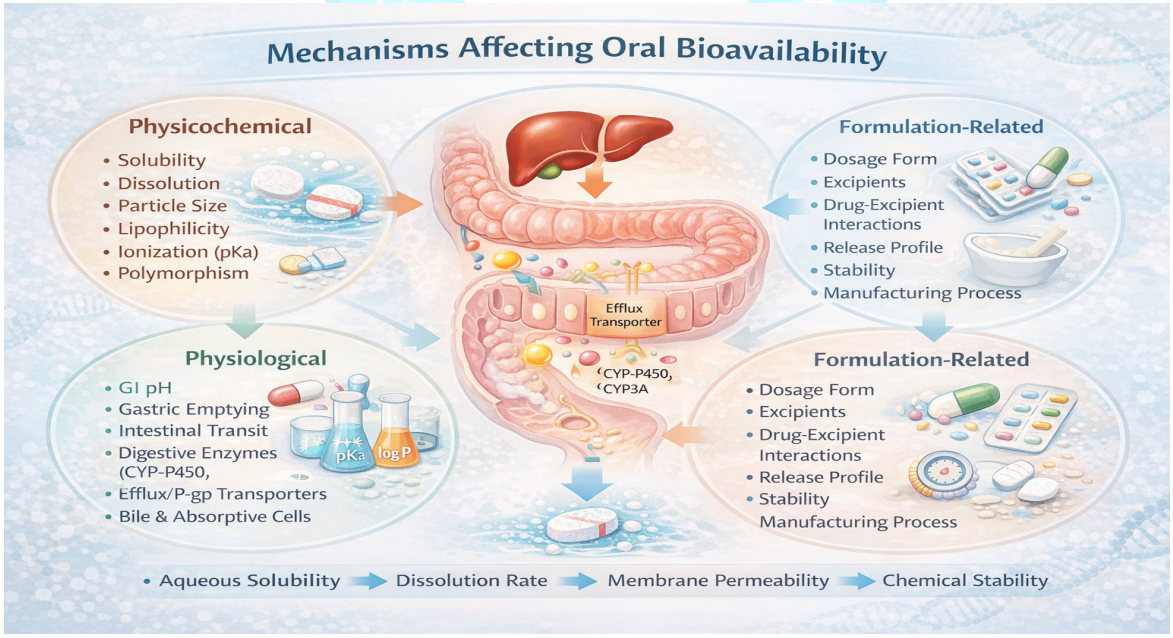

Fig 1: Mechanisms Affecting Oral Bioavailability

3. Limitations of Conventional Drug Delivery Systems

Due to their inherent limits in handling complex biopharmaceutical difficulties, conventional drug delivery systems, such as immediate-release tablets, capsules, and suspensions, frequently fail to provide optimal therapeutic outcomes. Their incapacity to improve the solubility and rate of dissolution of poorly water-soluble medications, which make up a significant portion of novel chemical entities, especially those categorized under Biopharmaceutics Classification System (BCS) Class II and IV, is a significant disadvantage (Amidon et al., 1995; Lipinski, 2000). Additionally, traditional formulations offer little defense against deterioration in the hostile gastrointestinal environment, which results in decreased systemic exposure, inconsistent absorption, and decreased stability (Dressman et al., 1998).

Furthermore, the bioavailability of medications with high metabolic clearance is further decreased by traditional systems' frequent inability to overcome significant first-pass metabolism and enzymatic degradation (Lennernández, 2007). Additionally, they are often subject to poor permeability and efflux transporter-mediated ejection, which results in inconsistent and low systemic availability, and they lack site-specific targeting capabilities (Singh et al., 2011). These difficulties highlight the urgent need for innovative drug delivery and design techniques that can get past biological obstacles, increase solubility and stability, and boost therapeutic efficacy.

Table 1: Comparison of Conventional vs. Novel Drug Delivery Systems

Feature	Conventional Systems	Novel Drug Delivery Systems (NDDS)	Example
Solubility enhancement	Limited	Improved via LBDDS, co-crystals, nanocarriers	Lipid-based formulations, solid dispersions
Targeted delivery	Poor	High, using ligands or stimuli-responsive carriers	Nanoparticles, prodrugs
Stability	Susceptible to degradation	Enhanced chemical and enzymatic stability	Prodrugs, polymeric systems
Bioavailability	Variable, often low	Significantly improved	Valacyclovir, enalapril, lipid nanoparticles

4. Novel Drug Design Approaches for Bioavailability Enhancement

4.1 Prodrug Design

Prodrug design is a tried-and-true method that temporarily alters the chemical structure of pharmacologically active molecules in order to increase their bioavailability. A prodrug is an inactive or less active derivative that, when administered, undergoes chemical or enzymatic biotransformation in vivo to produce the active parent drug (Testa & Krämer, 2007). This method works especially well for medications that have high first-pass metabolism, low membrane permeability, poor water solubility, or chemical instability (Rautio et al., 2008).

Prodrugs can improve gastrointestinal absorption, increase lipophilicity, and enable carrier-mediated transport across biological membranes by adding promoieties like esters, amides, or amino acids (Huttunen et al., 2011). The practical importance of this method is demonstrated by the greatly enhanced oral bioavailability of some clinically successful prodrugs, such as enalapril and valacyclovir, when compared to their parent molecules (Rautio et al., 2008). All things considered, prodrug design continues to be an effective and adaptable method for getting around biopharmaceutical restrictions and enhancing systemic drug exposure.

4.2 Molecular Modification Strategies

In order to improve bioavailability without compromising the pharmacological efficacy of the active moiety, molecular modification procedures entail purposeful changes to the physical characteristics of drug molecules. Improvements in water solubility, dissolution rate, chemical stability, and membrane permeability—all important factors influencing oral absorption—are the main focus of these strategies (Yalkowsky & He, 2003).

Because it can greatly improve solubility, dissolving behavior, and manufacturability while enhancing stability, salt production is one of these tactics that is frequently used for ionizable pharmaceuticals (Serajuddin, 2007). Precise control over solid-state characteristics, such as crystallinity and lattice energy, is made possible via polymorphic modification and crystal engineering, which directly affects dissolution and systemic exposure (Blagden et al., 2007). Furthermore, pharmaceutical co-crystals, which are created by noncovalent interactions between the active drug and appropriate co-formers, have shown promise as a way to improve

the drug's solubility, permeability, and physical stability without changing its molecular structure (Aakeröy et al., 2009).

These molecular alteration techniques have substantial clinical implications in addition to being highly adaptable from a research standpoint. They are frequently used in the creation of oral formulations for medications that are poorly soluble, allowing for better systemic exposure, less absorption fluctuation, and increased therapeutic efficacy. Bioavailability improvements can be further amplified by integration with contemporary drug delivery systems, such as lipid-based carriers or nanocarriers, providing a synergistic approach to overcoming biopharmaceutical challenges and enabling the successful translation of novel drug candidates into clinically effective therapies.

5. Novel Drug Delivery Systems (NDDS) for Bioavailability Enhancement

5.1 Lipid-Based Drug Delivery Systems (LBDDS)

Lipid-based drug delivery systems (LBDDS) are among the most widely used approaches for improving the bioavailability of poorly water-soluble drugs. These systems utilize oils, surfactants, and co-solvents to enhance drug solubilization, facilitate lymphatic transport, and bypass first-pass metabolism, thereby increasing systemic exposure (Porter et al., 2008). Common LBDDS include self-emulsifying drug delivery systems (SEDDS), self-microemulsifying drug delivery systems (SMEDDS), and nanoemulsions, which spontaneously form fine dispersions in gastrointestinal fluids, improving dissolution and absorption (Pouton, 2006).

Enhanced drug solubilization, defense against enzymatic degradation, increased intestinal permeability, and encouragement of chylomicron-mediated lymphatic transport—which helps medications avoid hepatic first-pass metabolism—are some of the ways that LBDDS improve bioavailability (Trevaskis et al., 2008). The clinical success of these systems is demonstrated by formulations like Neoral® (cyclosporine microemulsion), which shows better therapeutic efficacy and stable plasma levels when compared to traditional formulations. LBDDS provide a flexible and clinically proven platform for addressing the solubility and permeability constraints of contemporary treatments by fusing formulation design with lipid digestion and absorption mechanisms.

5.2 Polymeric and Nanocarrier Systems

Polymeric and nanocarrier systems have become flexible platforms for increasing the bioavailability of medications that are labile and poorly soluble. These systems, which can encapsulate medications, shield them from deterioration, and offer regulated or targeted release, include polymeric nanoparticles, dendrimers, polymeric micelles, and nanogels (Kreuter, 2001; Kumari et al., 2010). These carriers increase the surface area for dissolution, enhance solubility, and promote cellular uptake by bringing the particle size down to the nanometer range, which raises systemic exposure.

Biodegradable and biocompatible polymers including PLGA (polylactic-co-glycolic acid), chitosan, and PEGylated polymers can be used to create polymeric nanoparticles that provide customized drug release profiles and improved stability (Danhier et al., 2012). While polymeric micelles can solubilize hydrophobic pharmaceuticals in their hydrophobic core, enhancing solubility and absorption in the gastrointestinal tract, dendrimers' highly branched structure allows for precise drug loading, surface modification, and targeted delivery (Torchilin, 2007). These nanocarriers can also increase lymphatic absorption and avoid efflux transporters, which further improves oral bioavailability.

All things considered, polymeric and nanocarrier systems are a key component of contemporary drug administration techniques because they offer a versatile, scalable, and clinically transferable platform for resolving issues with solubility, stability, and permeability.

5.3 Vesicular Drug Delivery Systems

Lipid- or surfactant-based vesicular drug delivery systems are made up of one or more concentric bilayers that can encapsulate both lipophilic and hydrophilic medications, increasing their bioavailability. By enhancing membrane permeability, extending gastrointestinal residence duration, and shielding medications from enzymatic and chemical breakdown in the gastrointestinal tract, these systems enhance drug absorption (Uchegbu & Vyas, 1998). One of the most researched vesicular systems, liposomes are made of phospholipid bilayers and have shown great promise in enhancing the solubility, stability, and systemic availability of medications with low bioavailability (Allen & Cullis, 2013). They are appropriate for both oral and parenteral applications due to their biocompatibility and capacity to regulate medication release.

Niosomes and elastic vesicles like transfersomes and ethosomes, in addition to liposomes, have drawn a lot of interest for improving bioavailability. When compared to liposomes, niosomes—which are made of non-ionic surfactants—offer better chemical stability and cost-effectiveness while retaining a similar level of drug delivery efficiency (Moghassemi & Hadjizadeh, 2014). Because of their high deformability, transfersomes and ethosomes can more easily pass through biological barriers and improve medication penetration (Cevc & Blume, 2001). Vesicular drug delivery systems are useful tools in the development of sophisticated drug delivery techniques targeted at increasing bioavailability because they offer flexible and effective platforms for getting around solubility and permeability constraints.

5.4 Inclusion Complexes

Molecular assemblies known as inclusion complexes occur when a guest drug molecule is either fully or partially encased within the cavity of a host molecule, most frequently cyclodextrins, via noncovalent interactions such hydrogen bonds and van der Waals forces. By increasing the drug's perceived solubility, dissolving rate, and chemical stability without changing its intrinsic pharmacological activity, this method is frequently employed to increase the bioavailability of weakly water-soluble medications (Loftsson & Brewster, 2010). The hydrophobic central cavity and hydrophilic outer surface of cyclodextrins, such as α-, β-, and γ-cyclodextrins, and their chemically modified derivatives, such as hydroxypropyl-β-cyclodextrin and sulfobutyl ether-β-cyclodextrin, allow for the effective encapsulation of lipophilic drug molecules (Davis & Brewster, 2004).

By keeping the medication soluble at the absorption site and minimizing precipitation in the gastrointestinal environment, inclusion complex formation can further improve drug permeability (Loftsson et al., 2005). Furthermore, cyclodextrins can enhance formulation stability and shield medications from enzymatic degradation, resulting in more reliable and repeatable bioavailability (Carrier et al., 2007). Inclusion complexes are a reliable and clinically validated method for improving bioavailability in contemporary drug design systems because of their good safety profile, regulatory acceptance, and adaptability across oral, parenteral, and topical dose forms.

5.5 Solid-State Engineering Approaches

The goal of solid-state engineering techniques is to improve a drug's physical shape in order to increase its solubility, rate of dissolution, and, ultimately, oral bioavailability. To overcome the drawbacks of poorly water-soluble medications, strategies such solid dispersions, amorphous drug formulations, co-crystals, and particle size reduction are frequently used (Huang & Dai, 2014). According to Chiou and Riegelman (1971), solid dispersions, in which the medicine is molecularly dispersed in a hydrophilic carrier, increase wettability and decrease crystallinity, leading to quicker breakdown and improved absorption. Compared to their crystalline counterparts, amorphous formulations, which lack long-range crystal organization, usually show greater apparent solubility. However, stabilizing techniques are necessary to avoid recrystallization during storage (Hancock & Zografi, 1997).

Co-crystals can enhance solubility and stability while maintaining pharmacological activity when the active substance is combined with a pharmaceutically approved co-former through noncovalent interactions (Aakeröy et al., 2009). Furthermore, methods for reducing particle size, such micronization and nanonization, improve dissolving rates, increase surface area, and enable more uniform absorption (Möschwitzer, 2013). These methods offer a potent and scalable way to increase bioavailability by carefully modifying the solid-state characteristics of medications; they are frequently used in conjunction with other cutting-edge drug delivery systems for optimal therapeutic benefit.

Figure 2: Bioavailability Enhancement Strategies

Table 2: Representative Examples of Bioavailability-Enhancing Strategies

Strategy	Mechanism	Drug Examples	Key Benefits
Prodrug design	Biotransformation in vivo to active drug	Valacyclovir, Enalapril	Enhanced solubility, absorption, reduced first-pass effect
Salt formation	Increases solubility and dissolution	Diclofenac sodium, Furosemide	Improved oral absorption
Co-crystals	Noncovalent interactions with co-former	Carbamazepine–nicotinamide	Enhanced solubility and stability
Lipid-based systems	Solubilization in lipid matrix, lymphatic transport	Fenofibrate, Cyclosporine A	Increased bioavailability, reduced variability
Nanocarriers	Size-dependent permeability, protection from degradation	Paclitaxel nanoparticles, PLGA-drugs	Targeted delivery, prolonged circulation

6. Advanced and Emerging Drug Design Systems

6.1 Nanotechnology-Based Approaches

By offering incredibly adaptable platforms to address the solubility, permeability, and stability issues related to poorly bioavailable medications, nanotechnology-based methods have completely transformed drug delivery. These systems significantly increase surface area and dissolution rate by bringing drug particles down to the nanometer range, improving gastrointestinal absorption and overall bioavailability (Möschwitzer, 2013). Solid lipid nanoparticles (SLNs), polymeric nanoparticles, nanocrystals, nanoemulsions, and nanostructured lipid carriers (NLCs) are examples of common nanotechnology-based systems.

Without changing the medication's chemical composition, nanocrystals—pure drug nanoparticles supported by surfactants or polymers—offer enhanced solubility and quick dissolution (Tadros et al., 2004). According to Mason et al. (2006), nanoemulsions, which are usually oil-in-water systems with droplet sizes smaller than 200 nm, improve the solubilization of lipophilic medications, encourage lymphatic transport, and reduce first-pass metabolism. Additionally, sophisticated lipid and polymer-based nanosystems can enhance pharmacokinetic profiles, lower systemic toxicity, and deliver targeted and regulated drug release (Kreuter, 2014).

All things considered, nanotechnology-based methods are a fundamental component of contemporary drug design systems, allowing for the conversion of poorly soluble and labile chemicals into formulations that are both clinically and financially successful.

6.2 Biopharmaceutical Approaches

By modifying physiological barriers that restrict drug absorption, biopharmaceutical techniques seek to improve bioavailability. To increase intestinal absorption and extend the duration of medication residence at the absorption site, these tactics include the use of mucoadhesive systems, enzyme inhibitors, and permeation enhancers. Surfactants, fatty acids, and bile salts are examples of permeation enhancers that temporarily open tight junctions or change membrane fluidity to facilitate the paracellular and transcellular transport of poorly permeable medicines (Bernkop-Schnürch & Dünnhaupt, 2012). In order to increase systemic availability, enzyme inhibitors are used to shield medications from pre-systemic enzymatic breakdown, especially for peptide and protein therapies (Bruno et al., 2013). Mucoadhesive systems, which are made with polymers like chitosan or carbomers, stick to the gastrointestinal mucosa, extending the drug's residence duration and encouraging long-term absorption (Hassan & Gallo, 1990). Biopharmaceutical techniques work in tandem with formulation-based strategies to enhance oral bioavailability by addressing these physiological and biochemical limitations.

6.3 Smart and Targeted Drug Delivery Systems

Smart and targeted drug delivery systems are cutting-edge tactics intended to minimize systemic exposure and adverse effects while delivering medications precisely to their place of action. These methods enable fine spatiotemporal control over drug release by using stimuli-responsive carriers that release medications in response to environmental triggers including pH, temperature, redox potential, or enzymatic activity (Mura et al., 2013). For example, in the neutral-to-alkaline circumstances of the intestine or the acidic environment of the stomach, pH-sensitive polymers might release medications preferentially, improving the absorption and bioavailability of labile substances. Ligand-mediated techniques, in which carriers are functionalized with antibodies, peptides, or small molecules that recognize particular receptors on target cells, can also accomplish targeted delivery. This increases drug accumulation at the intended site and decreases off-target effects (Peer et al., 2007). To enhance circulation time,

stability, and controlled release kinetics, these systems can also be coupled with nanoscale platforms including liposomes, dendrimers, and polymeric nanoparticles (Torchilin, 2007). Together, intelligent and targeted delivery systems provide a state-of-the-art strategy in contemporary pharmaceutics, allowing for more effective and customized treatment via increased bioavailability and decreased toxicity.

7. Evaluation of Bioavailability Enhancement

An essential stage in evaluating the efficacy of innovative medication design and delivery methods is the assessment of bioavailability increase. To estimate the rate and degree of drug release and absorption, in vitro dissolution and permeability tests are frequently employed as preliminary screening methods. Dissolution testing provides information about how formulation changes affect solubility and release kinetics by simulating gastrointestinal circumstances (Dressman et al., 2007). Permeability studies evaluate a drug's capacity to cross biological membranes and identify potential absorption obstacles. They are frequently carried out using Caco-2 cell cultures or excised intestinal tissues (Artursson & Karlsson, 1991).

By tracking plasma drug concentrations over time following injection, in vivo pharmacokinetic assessment offers direct proof of systemic exposure. Bioavailability is measured and various formulations are compared using parameters such peak plasma concentration (C_max), time to attain peak concentration (T_max), and area under the plasma concentration–time curve (AUC) (Shargel et al., 2012).

Predicting in vivo performance based on in vitro results is made possible by the development of in vitro–in vivo correlation (IVIVC), which combines pharmacokinetic and dissolution data. Because IVIVC ensures therapeutic efficacy without requiring significant in vivo research, it is especially useful for formulation improvement, regulatory approval, and scale-up processes (Emami, 2006). When combined, these assessment instruments offer a thorough framework for confirming the efficacy of bioavailability improvement techniques in medication development.

Table 3: Evaluation Methods for Bioavailability Enhancement

Evaluation Parameter	Methodology	Outcome
In vitro dissolution	USP dissolution apparatus, simulated GI fluids	Assess drug release rate and solubility from formulations

Permeability studies	Caco-2 cell monolayer, PAMPA	Evaluate intestinal absorption potential
In vivo pharmacokinetics	Animal models, human bioavailability studies	Determine systemic exposure, Cmax, Tmax, AUC
In vitro–in vivo correlation (IVIVC)	Mathematical modeling, Level A/B/C correlation	Predict in vivo performance based on in vitro data
Stability studies	ICH guidelines (temperature, humidity, light)	Assess chemical and physical stability

8. Regulatory Considerations and Translational Challenges

To guarantee safety, effectiveness, and quality, the development of innovative drug design systems for bioavailability improvement must adhere to strict regulatory standards. To show that modified formulations offer consistent systemic exposure and therapeutic benefit without adding new risks, regulatory bodies like the European Medicines Agency (EMA) and the U.S. Food and Drug Administration (FDA) demand thorough pharmacokinetic, pharmacodynamic, and toxicological data (FDA, 2017; EMA, 2018). Since these factors can have a substantial impact on pharmacokinetics and biodistribution, regulators also place a strong emphasis on characterizing particle size, surface characteristics, stability, and potential immunogenicity in the context of nanotechnology-based or targeted delivery systems (Zhang et al., 2014).

The creation of sophisticated delivery systems is further complicated by translational issues. These include production scalability, physicochemical property repeatability, stability during storage, and patient physiology variability that may impact systemic availability and absorption (Kreuter, 2014). Furthermore, predictive preclinical models and strong in vitro–in vivo correlations (IVIVC) are essential for predicting clinical outcomes and optimizing dosage schedules. To successfully transfer laboratory advances into clinically viable treatments, an integrated approach including rigorous formulation design, quality control, and systematic pharmacological evaluation is needed to overcome these regulatory and translational obstacles.

9. Marketed Products and Case Studies

The effective application of bioavailability improvement techniques from research to clinical use is demonstrated by a number of commercially available medicinal drugs. For poorly water-

soluble medications, lipid-based formulations like Sandimmune® (cyclosporine conventional formulation) and Neoral® (cyclosporine microemulsion) demonstrate how self-emulsifying drug delivery systems (SEDDS) enhance solubility, absorption, and therapeutic consistency (Porter et al., 2008). Similar to this, liposomal formulations such as Doxil® (liposomal doxorubicin) reduce systemic toxicity while retaining efficacy by utilizing vesicular systems to improve drug stability, circulation time, and targeted delivery (Allen & Cullis, 2013).

As seen by Valacyclovir, the L-valyl ester prodrug of acyclovir, which enhances intestinal absorption and systemic exposure in comparison to the parent chemical, prodrug techniques have also successfully increased oral bioavailability (Rautio et al., 2008). Spironolactone–β-cyclodextrin complexes are an example of inclusion complexes that use cyclodextrins to improve oral bioavailability by improving solubility and dissolution (Loftsson & Brewster, 2010).

Clinical applications of polymeric and nanoparticle carriers to improve solubility, enable targeted distribution, and reduce side effects are demonstrated by advanced nanotechnology-based medicines such as Abraxane® (albumin-bound paclitaxel nanoparticles) (Gradishar et al., 2005). These case studies demonstrate how sophisticated drug delivery methods and logical formulation design can overcome biopharmaceutical constraints and produce notable clinical advantages, highlighting the translational potential of bioavailability augmentation tactics.

10. Future Perspectives and Emerging Trends

In order to address the drawbacks of poorly soluble and labile medications, the future of bioavailability augmentation depends on the integration of sophisticated formulation technologies, molecular design, and computational techniques. Multifunctional nanocarriers, stimuli-responsive systems, and intelligent targeted delivery platforms are examples of emerging techniques that allow for precise control over drug release, absorption, and site-specific administration (Mura et al., 2013; Torchilin, 2007). Furthermore, biopharmaceutical techniques like enzyme inhibitors, permeation enhancers, and mucoadhesive systems improve intestinal absorption, while prodrugs, inclusion complexes, and solid-state engineering continue to broaden the range of medications with enhanced solubility, stability, and permeability (Bruno et al., 2013; Loftsson & Brewster, 2010). It is anticipated that the integration of artificial intelligence and predictive modeling will shorten development times

and speed up the logical design of optimum formulations (Ekins et al., 2019). By bridging the gap between laboratory advances and commercially viable products, these multidisciplinary approaches collectively promise to produce safer, more effective, and patient-centric medicines.

11. Conclusion

Improving bioavailability is still a major problem in contemporary medication research, especially for molecules that are poorly soluble, unstable, or weakly permeable. This review emphasizes that biopharmaceutical barriers can be successfully overcome and systemic drug exposure enhanced by a multimodal approach that combines prodrug strategies, molecular modifications, novel drug delivery systems (lipid-based, polymeric, vesicular, inclusion complexes), solid-state engineering, and platforms based on nanotechnology. By focusing on physiological constraints, biopharmaceutical approaches such as mucoadhesive carriers, enzyme inhibitors, and permeation enhancers supplement formulation-based techniques. To guarantee clinical success, strict evaluation, strong in vitro–in vivo correlation, and scalable manufacturing are essential due to regulatory and translational considerations. New developments like AI-driven formulation design, multifunctional nanocarriers, and smart and stimuli-responsive systems promise to speed up the conversion of creative drug delivery techniques into safer, more efficient, and patient-centered treatments. When taken as a whole, these strategies show how rational drug design and cutting-edge delivery technology can optimize treatment outcomes and increase the clinical applicability of difficult pharmacological compounds.

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12. Conflict of Interest

The author declares no conflict of interest related to the content of this review.

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