

# A Comprehensive Mechanistic Review of Biopharmaceutical Barriers, Absorption Variability, and Advanced Formulation Strategies for Enhancing the Oral Bioavailability of BCS Class IV Drug Furosemide

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## ABSTRACT

For the treatment of edema and hypertension, furosemide is a commonly used loop diuretic; nonetheless, its oral administration is linked to a low and extremely variable bioavailability. Because of poor aqueous solubility, restricted intestinal permeability, and unpredictability related to absorption, a number of pharmacokinetic and biopharmaceutical investigations have revealed uneven therapeutic response after oral administration. Due to its classification as a Class IV medicine under the Biopharmaceutics Classification System (BCS), furosemide poses serious difficulties for oral drug delivery. Despite the comparatively restricted hepatic first-pass metabolism, reduced systemic availability is caused by presystemic variables like intestinal transport mechanisms, meal effect, and dissolution-limited absorption. To get around these restrictions, a number of formulation-based and route-based techniques have been studied, including as solid dispersions, parenteral or mucosal delivery, and nanosystems. This review compiles the body of research to identify the main biopharmaceutical issues with furosemide and highlights strategies that have shown promise in enhancing its therapeutic consistency and bioavailability.

**Keywords:** Furosemide; Biopharmaceutics Classification System; BCS Class IV; Oral Bioavailability; Drug Solubility; Intestinal Permeability; Pharmacokinetics; Solid Dispersions; Nanoparticles; Lipid-Based Systems; Cyclodextrin Complexes; Drug Absorption Variability.

## 1. Introduction

One of the most often recommended loop diuretics for the treatment of edema brought on by hepatic, renal, and cardiac conditions is furosemide. It is frequently utilized in both acute and chronic clinical circumstances because of its strong diuretic impact and quick beginning of action.

Oral furosemide administration frequently yields uneven therapeutic outcomes, despite its widespread clinical use. Low and extremely variable oral bioavailability, ranging from around 10% to 60%, has been described in clinical investigations. This results in an unpredictable diuretic response and frequent dose modifications.

The goal of this paper is to provide an overview of the biopharmaceutical factors that contribute to furosemide's low oral bioavailability, with a focus on presystemic factors, solubility and permeability restrictions, and its BCS classification.

Furthermore, covered are formulation-based and route-based approaches investigated to enhance furosemide's bioavailability.

### 1.1. Study Objective

The objectives of this study are:

- 1) To examine the physicochemical characteristics affecting the absorption of furosemide.
- 2) To assess the pharmacological obstacles that impact oral bioavailability.
- 3) To investigate the effects of presystemic and gastrointestinal variables.

- 4) To examine formulation-based methods for improving bioavailability.
- 5) To investigate different medication delivery methods.
- 6) To determine potential avenues for future medication delivery studies.

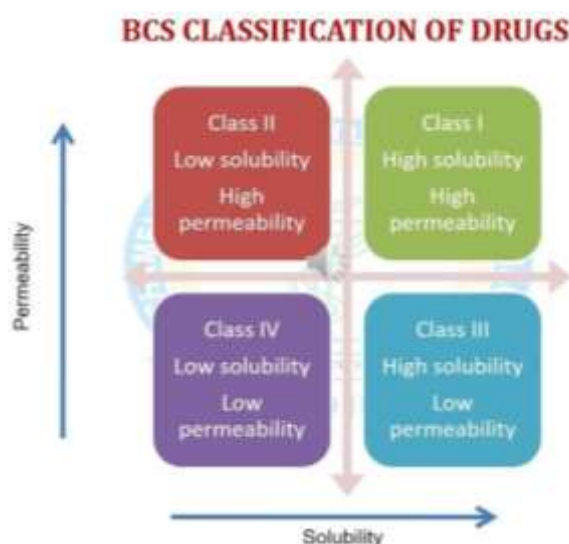
## 2. Literature Review

### 2.1. Drug Profile and Biopharmaceutics Classification of Furosemide.

A sulfonamide-derived loop diuretic, furosemide is commonly used to treat edema and hypertension caused by congestive heart failure, renal impairment, and hepatic cirrhosis. It enhances the excretion of water, sodium, and chloride by inhibiting the  $\text{Na}^+ - \text{K}^+ - 2\text{Cl}^-$  cotransporter in the thick ascending limb of the loop of Henle. According to physicochemical analysis, furosemide has a molecular weight of 330.74 g/mol and a pKa of roughly 3.9, making it a slightly acidic substance. Its poor aqueous solubility and pH-dependent dissolving behavior have a major impact on how well the gastrointestinal tract absorbs it. After oral administration, the medication's weak solubility in stomach fluid causes incomplete dissolution.

The Biopharmaceutics Classification System (BCS) classifies furosemide as a Class IV medication because of its low intestinal permeability and low solubility. Since both dissolution and membrane penetration serve as limiting factors in drug absorption, medications in this class pose the most challenge for oral drug administration. The limited and highly variable oral bioavailability of furosemide can be explained scientifically by its BCS Class IV character. Poor permeability across the intestinal epithelium further reduces systemic uptake, resulting in uneven plasma drug concentrations and a varied therapeutic response. Inadequate solubility further lowers the amount of medicine available for absorption.

This section is justified since furosemide's poor solubility, limited permeability, and irregular absorption can only be explained by an understanding of its physicochemical characteristics and Biopharmaceutics Classification System (BCS) category. These features provide the scientific justification for the medication's poor oral bioavailability.



**Figure 1.** BCS Classification of Drugs

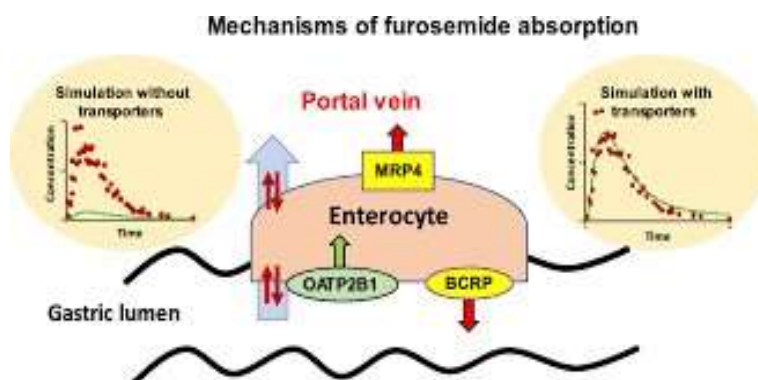
**Table 1.** Furosemide's Physicochemical and Biopharmaceutical Characteristics

Parameter	Description
Drug Class	Loop Diuretic
Chemical Nature	Sulfonamide Derivative
Molecular Weight	330.74 g/mol
Pka	~3.9
Aqueous Solubility	Poor
Intestinal Permeability	Low
Oral Bioavailability	10–60% (variable)
BCS Classification	Class IV
Route of Administration	Oral, Intravenous

The physicochemical characteristics listed in Table 1 emphasize the permeability and solubility restrictions that cause furosemide to perform poorly when taken orally.

## 2.2. Biopharmaceutical Factors Influencing Furosemide's Oral Uptake

The low and erratic oral bio accessibility of furosemide is caused by a number of biopharmaceutical variables. These characteristics mainly include presystemic elimination, gastrointestinal transit variability, reduced intestinal permeability, and solubility-limited dissolution.


**Figure 2.** The Furosemide Absorption pathway

### 2.2.1. Poor Solubility in Water

Low aqueous solubility is a characteristic of furosemide, especially in acidic environments like the stomach. The amount of medicine available in solution for absorption is thereby limited as a result of the drug's inadequate breakdown after oral delivery. Poor solubility drastically lowers the percentage of medicine that can be absorbed from the gastrointestinal system because dissolving is a need for absorption.

### 2.2.2. Low Permeability of the Intestines

Furosemide exhibits restricted permeability across the intestinal epithelium in addition to its poor solubility. Only a tiny portion of the medication can pass through the intestinal wall and enter the bloodstream, even after being dissolved. One of the main features of BCS Class IV medications is their permeability-limited absorption, which significantly lowers their oral bioavailability.

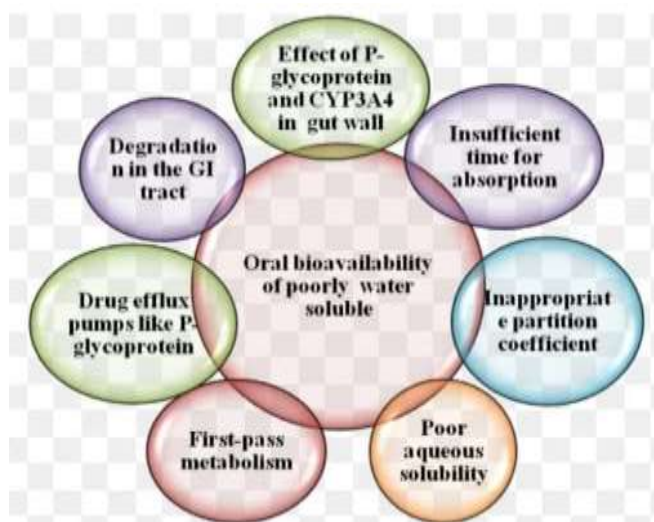
### 2.2.3. Food Effect and Variable Gastric Emptying

The absorption of furosemide is significantly influenced by the presence of food and the time it takes for the stomach to empty. Drug absorption and solubility are further hampered by eating since it slows down stomach emptying and alters the pH of the gastrointestinal system. As a result, it has been shown that taking oral furosemide with meals lowers the pace and degree of absorption, which delays and lessens the therapeutic effect.

### 2.2.4. Elimination Before Systemic

Despite the comparatively modest hepatic first-pass metabolism of furosemide, presystemic clearance in the gastrointestinal tract reduces systemic availability. Furthermore, the percentage of oral medication that enters the systemic circulation is further restricted by intestinal transport systems and local metabolism. Because these factors together control the degree and variability of oral medication absorption, it is justified to examine biopharmaceutical factors such as solubility, intestinal permeability, dietary influence, and presystemic elimination. Understanding these restrictions aids in determining the reasons behind the irregular therapeutic response seen with oral furosemide.

The series of biopharmaceutical elements that contribute to furosemide's decreased and fluctuating oral bioavailability is depicted in Figure 3.



**Figure 3.** Factors Affecting Furosemide's Poor Oral Bioavailability

## 3. Methodology

This review study was conducted using a systematic approach to collect and analyze relevant scientific literature related to furosemide and its oral bioavailability. Data were obtained from reliable academic sources including PubMed, ScienceDirect, Google Scholar, and standard pharmaceutical textbooks.

Relevant articles were selected based on their focus on biopharmaceutical properties, pharmacokinetics, solubility, intestinal permeability, and formulation strategies aimed at improving the bioavailability of furosemide. Priority was given to peer-reviewed journal articles and recent studies to ensure the accuracy and relevance of the information.

The collected literature was critically analyzed and organized into key thematic areas such as physicochemical properties, biopharmaceutical limitations, and advanced drug delivery systems. The findings were then synthesized to provide a comprehensive understanding of the challenges and potential solutions associated with improving the oral bioavailability of furosemide.

## **4. Result and Discussion**

### **4.1. Methods Based on Formulation**

Several formulation-based solutions have been studied to improve the solubility, dissolution rate, and intestinal absorption of standard oral furosemide tablets in order to overcome their biopharmaceutical constraints.

#### **Dispersions of Solids**

By improving wettability and decreasing crystallinity, solid dispersion techniques employing hydrophilic carriers have been shown to increase the percentage of medication available for absorption and improve the dissolution rate of furosemide.

#### **Systems Based on Nanotechnology**

Furosemide nanoparticles and nanosuspensions have shown notable improvements in oral bioavailability and dissolving behavior because of their larger surface area and better capacity to interact with gastrointestinal fluids.

#### **Drug Delivery Systems Based on Lipids**

To increase furosemide's solubility and encourage lymphatic uptake, self-emulsifying and lipidbased delivery methods have been investigated. This will increase systemic exposure.

#### **Complexes of Cyclodextrin Inclusion**

It has been demonstrated that cyclodextrin complexation improves furosemide's water solubility and stability, resulting in better absorption and dissolving properties.

### **4.2. Methods Based on Routes**

To get over gastrointestinal and absorption-related restrictions, alternate routes of administration have been investigated in addition to formulation changes.

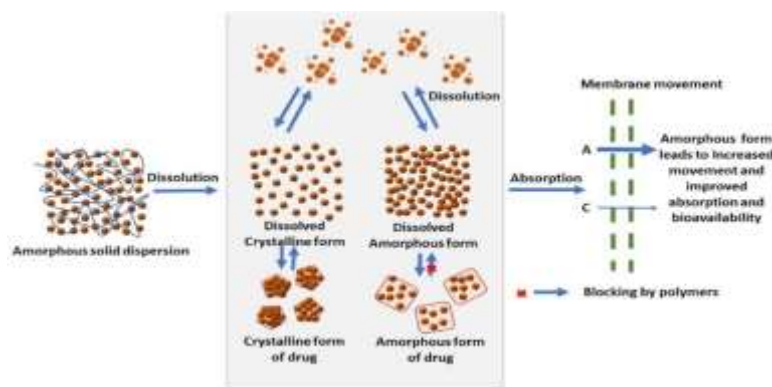
#### **Administration by Parenteral**

Furosemide has a complete bioavailability and a quick onset of action when administered intravenously, which makes it appropriate for acute and emergency clinical situations.

#### **Delivery of Buccal and Sublingual**

In order to circumvent gastrointestinal breakdown and first-pass metabolism, buccal and sublingual formulations have been studied. This offers a quicker onset and more consistent systemic absorption.

The purpose of this section is to evaluate the different formulation-based and route-based strategies that have been studied to get around furosemide's biopharmaceutical constraints. These tactics show how solubility, absorption, and total bioavailability can all be improved by thoughtful drug delivery design.



**Figure 4.** Schematic presentation of overall enhancement of solubility and bioavailability by amorphous solid dispersions

**Table 2.** Methods Examined to Increase Furosemide's Bioavailability

Strategy	Approach	Outcome
Solid dispersions	Polymer carriers	Increase Dissolution
Nanoparticles	Particle size reduction	Increase Bioavailability
Lipid based systems	Solubilization	Increase Absorption
Cyclodextrin complexes	Inclusion complex	Increase Solubility
IV administration	Route modification	100% Bioavailability

The many formulation and route-based techniques investigated to get around furosemide's bioavailability restrictions are highlighted in Table 2.

## 5. Conclusion

Although furosemide is still a clinically significant loop diuretic, its poor and extremely variable absorption limits its therapeutic efficacy after oral dosing. Low aqueous solubility, restricted intestinal permeability, and absorption-related parameters consistent with BCS Class IV features are the main causes of these limits, according to a study of published literature. A variety of formulation-based techniques, including as lipid formulations, cyclodextrin complexes, solid dispersions, and nanotechnology-based systems, have shown promise in improving furosemide absorption and dissolution. Additionally, alternate administration methods like buccal and intravenous delivery provide a quicker onset of effect and greater predictability. All things considered, overcoming the biopharmaceutic difficulties related to furosemide and achieving reliable therapeutic results require adjustment of the dosage form and administration method.

### 5.1. Future Recommendations

- 1) Further research should focus on the development of advanced nanocarrier systems to enhance drug solubility and absorption.
- 2) More in vivo and clinical studies are needed to validate the effectiveness of novel formulation strategies.
- 3) Exploration of targeted and personalized drug delivery approaches could help reduce variability in patient response.

- 4) Greater emphasis should be placed on lipid-based and self-emulsifying drug delivery systems for improved bioavailability.
- 5) Alternative routes such as buccal, transdermal, or pulmonary delivery should be further investigated.
- 6) Future studies should aim to bridge the gap between laboratory findings and real-world clinical application.

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#### **Competing Interests Statement**

The authors have not declared any conflict of interest.

#### **Consent for publication**

The authors declare that they consented to the publication of this study.

#### **Authors' contributions**

All authors contributed equally.

#### **Informed Consent**

Not applicable for this study.

#### **Availability of data and material**

Supplementary information is available from the authors upon request.

#### **Institutional Review Board Statement**

Not applicable for this study.

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#### **Declaration of AI**

AI tools were used for language editing.

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