INTERNATIONAL JOURNAL OF PHARMACEUTICAL SCIENCES
[ISSN: 0975-4725; CODEN(USA): IJPS00]
Journal Homepage: https://www.ijpsjournal.com

OPEN ACCESS

Review Article

Formulation Strategies to Enhance the Bioavailability of BCS Class-II Antidiabetic Drugs: Current Advances and Future Perspectives

Chetan Jain*[1], Dr. Vaibhavkumar Jagtap[2]

[1] *DCS's A.R.A College of Pharmacy, Nagaon, Dhule.*
[2] *NES's Gangamai College of Pharmacy, Nagaon, Dhule.*

ARTICLE INFO

Published: 23 Jun 2026

Keywords:
Diabetes mellitus, BCS Class-II drugs, antidiabetic drugs, oral bioavailability, solubility enhancement, nanoemulsions, SNEDDS, nanostructured lipid carriers, polymeric nanocarriers, drug delivery systems.

DOI:
10.5281/zenodo.20815200

ABSTRACT

Diabetes mellitus is a chronic metabolic disorder characterized by elevated blood glucose levels and remains a major global health concern. Several widely used oral antidiabetic drugs, including glibenclamide, glimepiride, pioglitazone, and repaglinide, belong to the Biopharmaceutics Classification System (BCS) Class-II category, exhibiting low aqueous solubility and high permeability. Poor solubility limits drug dissolution and absorption, resulting in reduced and variable oral bioavailability. To overcome these challenges, various formulation strategies have been developed, including micronization, nanonization, solid dispersions, and crystal engineering. Advanced drug delivery systems such as self-emulsifying drug delivery systems (SEDDS), self-nanoemulsifying drug delivery systems (SNEDDS), nanoemulsions, solid lipid nanoparticles (SLNs), nanostructured lipid carriers (NLCs), polymeric nanoparticles, and nanosuspensions have shown significant potential in enhancing solubility and bioavailability. Recent studies demonstrate that lipid-based and nanotechnology-driven formulations improve pharmacokinetic performance and therapeutic efficacy. Future advancements involving Quality by Design (QbD), artificial intelligence, and multifunctional nanocarriers may further optimize antidiabetic drug delivery and treatment outcomes.

INTRODUCTION

1.1 Diabetes Mellitus: A Global Health Challenge

Diabetes mellitus (DM) is a chronic metabolic disorder characterized by persistent hyperglycemia resulting from defects in insulin secretion, insulin action, or both. It represents one of the most significant public health challenges worldwide due to its increasing prevalence and associated complications (International Diabetes Federation [IDF], 2021). According to the IDF Diabetes Atlas, approximately 537 million adults

---

***Corresponding Author:** Chetan Jain
Address: *DCS's A.R.A College of Pharmacy, Nagaon, Dhule*
Email ✉: cvj5395@gmail.com

Relevant conflicts of interest/financial disclosures: The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

aged 20–79 years were living with diabetes in 2021, and this number is projected to increase to 643 million by 2030 and 783 million by 2045 (IDF, 2021).

Type 2 diabetes mellitus (T2DM) accounts for nearly 90–95% of all diabetes cases and is closely associated with obesity, sedentary lifestyle, unhealthy dietary habits, and aging populations (American Diabetes Association [ADA], 2024). The disease is associated with various microvascular and macrovascular complications, including diabetic nephropathy, retinopathy, neuropathy, coronary artery disease, and stroke, leading to substantial morbidity and mortality worldwide (Forbes & Cooper, 2013).

Oral antidiabetic therapy remains the first-line treatment for most patients with T2DM due to its convenience, cost-effectiveness, and improved patient compliance (ADA, 2024). However, the therapeutic effectiveness of several oral antidiabetic agents is often compromised by poor aqueous solubility and low oral bioavailability, necessitating the development of advanced formulation approaches (Kalepu & Nekkanti, 2015).

Table 1: Global Prevalence and Projected Growth of Diabetes Mellitus (2021–2045) (International Diabetes Federation [IDF], 2021)

Year	Adults with Diabetes (Millions)	Global Prevalence (%)	Source
2021	537	10.5	IDF Diabetes Atlas (2021)
2030	643	11.3	IDF Diabetes Atlas (2021)
2045	783	12.2	IDF Diabetes Atlas (2021)

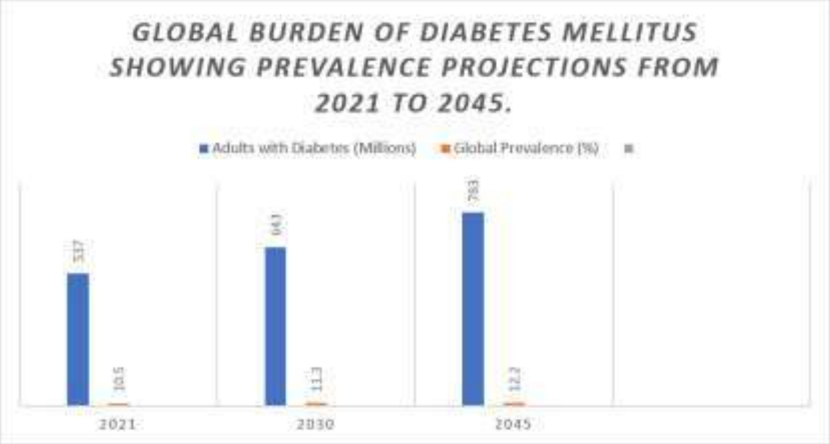


Figure 1: Global burden of diabetes mellitus showing prevalence projections from 2021 to 2045.

1.2 Oral Drug Delivery and Bioavailability Challenges

Oral administration remains the most preferred route of drug delivery because of its ease of administration, non-invasive nature, patient acceptance, and suitability for chronic therapy (Patel et al., 2020). Nevertheless, successful oral drug delivery requires adequate dissolution of the drug in gastrointestinal fluids followed by permeation across the intestinal epithelium into systemic circulation (Amidon et al., 1995).

Bioavailability refers to the rate and extent to which an active pharmaceutical ingredient reaches systemic circulation and becomes available at the site of action (Shargel & Yu, 2016). Several physiological and physicochemical factors influence oral bioavailability, including aqueous solubility, dissolution rate, intestinal permeability, gastrointestinal pH, gastric emptying time, metabolism, and transporter-mediated drug efflux (Savjani et al., 2012).

Poor aqueous solubility is recognized as one of the major obstacles in oral drug delivery. It has been estimated that nearly 40% of marketed drugs and approximately 70–90% of newly discovered drug molecules exhibit poor water solubility (Kalepu & Nekkanti, 2015). Inadequate solubility often results in slow dissolution rates, incomplete absorption, and high variability in therapeutic response (Dressman & Reppas, 2020).

For antidiabetic drugs with low aqueous solubility, insufficient dissolution in gastrointestinal fluids significantly limits the amount of drug available for absorption, ultimately reducing therapeutic efficacy and increasing inter-patient variability (Patel et al., 2020).

Table 2: Physiological and physicochemical factors affecting oral bioavailability.

Factor	Category	Impact on Bioavailability
Aqueous Solubility	Physicochemical	Influences drug dissolution
Dissolution Rate	Physicochemical	Controls amount available for absorption
Particle Size	Physicochemical	Smaller particles improve dissolution
Lipophilicity (Log P)	Physicochemical	Affects membrane permeation
pKa	Physicochemical	Determines ionization and absorption
Gastric Emptying Time	Physiological	Influences residence time
Intestinal Transit Time	Physiological	Affects absorption window
Gastrointestinal pH	Physiological	Influences solubility
Food Effect	Physiological	May increase or decrease absorption
First-Pass Metabolism	Biological	Reduces systemic availability
Efflux Transporters (P-gp)	Biological	Decrease drug absorption
Metabolic Enzymes (CYP450)	Biological	Increase drug elimination

1.3 Biopharmaceutical Classification System (BCS)

The Biopharmaceutical Classification System (BCS) was proposed by Amidon et al. (1995) to classify drug substances according to their aqueous solubility and intestinal permeability characteristics. The BCS provides a scientific framework for predicting oral drug absorption and guiding formulation development strategies.

According to the BCS, drugs are classified into four categories:

- Class I: High solubility and high permeability
- Class II: Low solubility and high permeability
- Class III: High solubility and low permeability
- Class IV: Low solubility and low permeability (Amidon et al., 1995)

Among these categories, BCS Class-II drugs present significant formulation challenges because their absorption is primarily limited by dissolution rather than permeability (Takagi et al., 2006). Although these drugs possess excellent membrane permeability, their poor aqueous solubility delays dissolution in gastrointestinal fluids, thereby limiting systemic absorption (Savjani et al., 2012).

The dissolution behavior of poorly soluble drugs can be explained by the Noyes–Whitney equation, which states that dissolution rate is directly proportional to surface area and saturation solubility (Noyes & Whitney, 1897). Consequently, formulation approaches aimed at increasing surface area, improving wettability, or enhancing saturation solubility can significantly improve bioavailability.

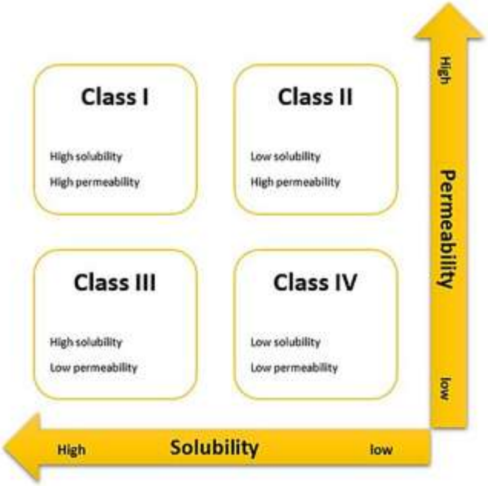


Figure 2: Biopharmaceutical Classification System (BCS) matrix.

Table 3: Characteristics and examples of BCS Classes I–IV drugs.

BCS Class	Solubility	Permeability	Absorption Limitation	Examples
Class I	High	High	None	Metformin, Paracetamol
Class II	Low	High	Dissolution Limited	Glibenclamide, Glimepiride, Pioglitazone
Class III	High	Low	Permeability Limited	Cimetidine, Atenolol
Class IV	Low	Low	Solubility and Permeability Limited	Hydrochlorothiazide

1.4 BCS Class-II Antidiabetic Drugs and Their Limitations

Several commonly prescribed oral antidiabetic agents belong to BCS Class-II because of their poor aqueous solubility and high membrane permeability. These include glibenclamide, glimepiride, pioglitazone, and repaglinide (Dahan et al., 2009).

Glibenclamide exhibits very low aqueous solubility, which contributes to dissolution-limited absorption and variable bioavailability (Sweetman, 2020). Similarly, glimepiride possesses poor water solubility, resulting in delayed dissolution and inconsistent plasma concentrations (Kawabata et al., 2011).

Pioglitazone, a thiazolidinedione derivative, demonstrates low aqueous solubility and undergoes extensive hepatic metabolism, which further contributes to variability in systemic drug exposure (Patel et al., 2020). Repaglinide, despite exhibiting rapid absorption, suffers from dissolution-related limitations due to its hydrophobic nature (Dahan et al., 2009).

The major challenges associated with BCS Class-II antidiabetic drugs include:

- Poor aqueous solubility
- Slow dissolution rate
- Variable gastrointestinal absorption
- Food-dependent bioavailability

- Delayed onset of therapeutic action
- Increased inter-subject variability

These limitations often necessitate higher doses and frequent administration, increasing the likelihood of adverse effects and compromising patient adherence (Kalepu & Nekkanti, 2015).

Table 4: Physicochemical properties of BCS Class-II antidiabetic drugs.

Drug	Molecular Weight (g/mol)	Log P	Water Solubility	pKa	Half-Life (h)	BCS Class
Glibenclamide	494.0	4.8	0.004 mg/mL	5.3	10	II
Glimepiride	490.6	3.2	0.004 mg/mL	6.2	5–8	II
Pioglitazone	356.4	2.3	0.04 mg/mL	5.2	3–7	II
Repaglinide	452.6	3.8	0.034 mg/mL	4.2	1	II

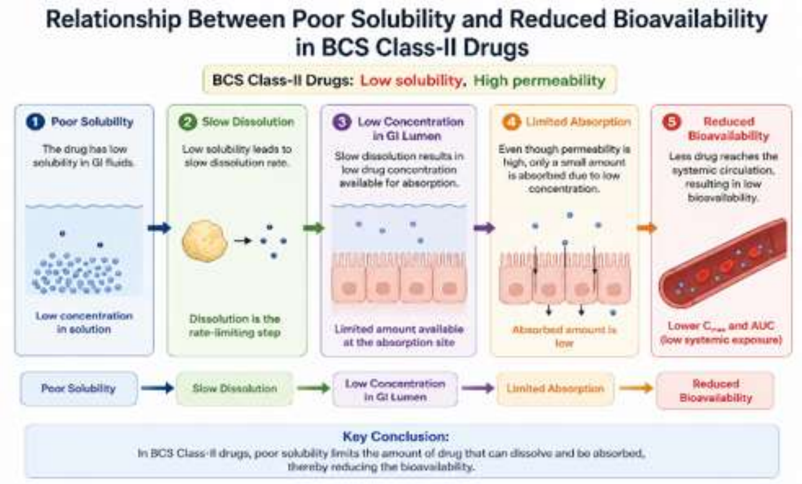


Figure 3: Relationship between poor solubility and reduced bioavailability in BCS Class-II drugs.

1.5 Formulation Strategies for Bioavailability Enhancement

To overcome the challenges associated with BCS Class-II antidiabetic drugs, numerous formulation strategies have been investigated. Conventional techniques include micronization, nanosizing, crystal engineering, salt formation, and solid dispersion technology (Savjani et al., 2012).

Recent advances in nanotechnology have enabled the development of sophisticated drug delivery systems capable of significantly improving drug solubility and oral bioavailability. These systems include nanoemulsions, self-emulsifying drug delivery systems (SEDDS), self-nanoemulsifying drug delivery systems (SNEDDS), solid lipid nanoparticles (SLNs), nanostructured lipid carriers (NLCs), polymeric nanoparticles, liposomes, and nanosuspensions (Patel et al., 2020).

Among these approaches, nanoemulsion-based systems have attracted considerable attention due to their ability to improve drug solubilization, enhance intestinal permeability, increase surface area, and facilitate lymphatic uptake (Sharma & Jain, 2018). Several studies have reported significant enhancement in the oral bioavailability of glibenclamide, glimepiride, and pioglitazone through nanoemulsion formulations (Patel et al., 2020).

1.6 Scope and Objective of the Review

Given the increasing prevalence of diabetes mellitus and the formulation challenges associated with poorly soluble antidiabetic drugs, there is a pressing need to evaluate available formulation strategies for enhancing oral bioavailability. This review critically discusses conventional and advanced formulation approaches employed for BCS Class-II antidiabetic drugs, with particular emphasis on nanoemulsions, lipid-based delivery systems, and nanotechnology-driven drug delivery platforms.

Furthermore, the review summarizes recent advancements, comparative effectiveness of different formulation strategies, regulatory considerations, commercialization challenges, and future research opportunities in the field of oral antidiabetic drug delivery.

2. OVERVIEW OF BCS CLASS-II ANTIDIABETIC DRUGS

2.1 Characteristics of BCS Class-II Drugs

The Biopharmaceutical Classification System (BCS) categorizes drug molecules based on their aqueous solubility and intestinal permeability characteristics. According to the BCS proposed by Amidon et al. (1995), Class-II drugs are characterized by low aqueous solubility and high membrane permeability. For these compounds, the rate-limiting step in oral absorption is drug dissolution rather than permeation across the gastrointestinal membrane. Consequently, improving solubility and dissolution rate is critical for enhancing their oral bioavailability.

Many modern therapeutic agents belong to BCS Class-II because advances in medicinal chemistry often favor highly lipophilic molecules with strong receptor-binding affinity. However, increased lipophilicity generally results in poor aqueous solubility, creating significant formulation challenges (Kalepu & Nekkanti, 2015). It is estimated that approximately 40% of marketed drugs and nearly 70–90% of new chemical entities exhibit poor aqueous solubility, emphasizing the importance of solubility enhancement technologies in pharmaceutical development (Savjani et al., 2012).

Low Aqueous Solubility

Aqueous solubility refers to the maximum amount of drug that can dissolve in a given volume of water under specified conditions. BCS Class-II drugs exhibit limited water solubility because of their hydrophobic molecular structures, high crystallinity, and strong intermolecular interactions within the crystal lattice (Kawabata et al., 2011).

Poor aqueous solubility directly affects the dissolution behavior of oral dosage forms. Since only dissolved drug molecules can permeate biological membranes, inadequate dissolution results in reduced absorption and suboptimal therapeutic efficacy. The challenge becomes more pronounced in antidiabetic drugs that require consistent plasma concentrations for effective glycemic control.

High Membrane Permeability

Despite poor solubility, BCS Class-II drugs generally possess high intestinal permeability due to their lipophilic nature. High permeability allows these molecules to readily diffuse across biological membranes once dissolved in gastrointestinal fluids (Amidon et al., 1995).

The permeability of a drug is often correlated with its partition coefficient (Log P). Drugs with moderate to high Log P values demonstrate greater membrane partitioning and transcellular transport. Antidiabetic agents such as glibenclamide, glimepiride, pioglitazone, and repaglinide possess favorable permeability characteristics but remain limited by dissolution rate.

Dissolution-Limited Absorption

For BCS Class-II drugs, oral absorption is primarily controlled by dissolution kinetics. The relationship between dissolution rate and drug absorption can be explained by the Noyes–Whitney equation, which states that dissolution rate increases with surface area and saturation solubility (Noyes & Whitney, 1897).

Since dissolution is the rate-limiting step, formulation strategies that increase drug surface area, improve wettability, reduce crystallinity, or enhance saturation solubility can significantly improve bioavailability. Consequently, BCS Class-II drugs are ideal candidates for advanced drug delivery systems such as nanoemulsions, self-emulsifying systems, nanosuspensions, and lipid nanoparticles (Porter et al., 2007).

Table 5: Comparison of BCS Classes and Absorption Characteristics

BCS Class	Solubility	Permeability	Limiting Factor
I	High	High	None
II	Low	High	Dissolution
III	High	Low	Permeability
IV	Low	Low	Solubility and Permeability

2.2 Common BCS Class-II Antidiabetic Drugs

Several widely prescribed oral antidiabetic agents belong to BCS Class-II and exhibit poor aqueous solubility despite possessing excellent membrane permeability.

Glibenclamide (Glyburide)

Glibenclamide is a second-generation sulfonylurea that stimulates insulin secretion from pancreatic β-cells. Although highly potent, it exhibits extremely poor aqueous solubility (approximately 0.004 mg/mL), resulting in dissolution-limited absorption and variable bioavailability (Sweetman, 2020).

Numerous formulation strategies including solid dispersions, nanosuspensions, and nanoemulsions have been investigated to improve the dissolution behavior of glibenclamide.

Glimepiride

Glimepiride is another second-generation sulfonylurea used extensively in the treatment of Type 2 diabetes mellitus. Similar to glibenclamide, glimepiride exhibits poor aqueous solubility and belongs to BCS Class-II (Kawabata et al., 2011).

Studies have shown that nanotechnology-based delivery systems can significantly enhance the dissolution rate and oral absorption of glimepiride.

Pioglitazone

Pioglitazone belongs to the thiazolidinedione class and acts by improving insulin sensitivity through activation of peroxisome proliferator-activated receptor gamma (PPAR-γ). Despite its therapeutic efficacy, pioglitazone exhibits limited water solubility and undergoes extensive hepatic metabolism, contributing to variable bioavailability (Patel et al., 2020).

Lipid-based formulations and nanoemulsion systems have demonstrated substantial improvements in the bioavailability of pioglitazone.

Repaglinide

Repaglinide is a meglitinide derivative characterized by rapid onset and short duration of action. The drug exhibits poor aqueous solubility but favorable membrane permeability, making it an ideal candidate for solubility enhancement technologies (Dahan et al., 2009).

Table 6: Physicochemical Properties of Common BCS Class-II Antidiabetic Drugs

Drug	Molecular Weight (g/mol)	Solubility (mg/mL)	Log P	pKa	BCS Class
Glibenclamide	494.0	0.004	4.8	5.3	II
Glimepiride	490.6	0.004	3.2	6.2	II
Pioglitazone	356.4	0.04	2.3	5.2	II
Repaglinide	452.6	0.034	3.8	4.2	II

2.3 Pharmacokinetic Limitations

Slow Dissolution

The primary pharmacokinetic limitation of BCS Class-II drugs is slow dissolution within gastrointestinal fluids. Poor dissolution delays drug absorption and reduces the amount of drug reaching systemic circulation (Dressman & Reppas, 2020).

Variable Absorption

Variability in gastrointestinal pH, gastric emptying rate, and intestinal transit time contributes to inconsistent absorption patterns among patients. This variability often results in fluctuating plasma drug concentrations and unpredictable therapeutic outcomes.

Food Effect

Food intake can significantly influence the absorption of poorly soluble drugs. High-fat meals may enhance the solubilization of lipophilic drugs, whereas certain foods may delay gastric emptying and alter dissolution behavior (Porter et al., 2007).

First-Pass Metabolism

Several BCS Class-II antidiabetic drugs undergo extensive hepatic metabolism before reaching systemic circulation. This first-pass effect further reduces oral bioavailability and contributes to inter-individual variability in therapeutic response.

Table 7: Pharmacokinetic Limitations of BCS Class-II Antidiabetic Drugs

Limitation	Mechanism	Clinical Impact
Slow Dissolution	Poor aqueous solubility	Reduced absorption
Variable Absorption	GI variability	Inconsistent efficacy
Food Effect	Altered solubilization	Variable plasma levels
First-Pass Metabolism	Hepatic drug loss	Reduced bioavailability

2.4 Clinical Consequences

The poor aqueous solubility and dissolution-limited absorption of BCS Class-II antidiabetic drugs have important clinical implications.

Reduced Therapeutic Efficacy

Incomplete dissolution may prevent attainment of optimal plasma drug concentrations, reducing therapeutic effectiveness and compromising glycemic control.

Dose Variability

Variability in absorption often necessitates dose adjustments and individualized therapy, particularly in patients with altered gastrointestinal physiology.

Increased Side Effects

Higher doses are frequently required to compensate for poor bioavailability. Increased dosing may elevate the risk of adverse effects, including hypoglycemia in sulfonylurea-treated patients.

Reduced Patient Compliance

Frequent dose adjustments and inconsistent therapeutic outcomes may negatively impact patient adherence and long-term disease management.

Table 8: Clinical Consequences of Poor Bioavailability in BCS Class-II Antidiabetic Drugs

Challenge	Clinical Outcome
Poor Dissolution	Reduced efficacy
Variable Absorption	Inconsistent glycemic control
High Dose Requirement	Increased side effects
Food Effect	Variable therapeutic response
Bioavailability Variability	Reduced patient compliance

3. MECHANISMS LIMITING BIOAVAILABILITY OF BCS CLASS-II DRUGS

3.1 Drug Solubility Issues

Oral bioavailability is largely dependent on the ability of a drug to dissolve in gastrointestinal fluids before permeating the intestinal membrane. Although BCS Class-II drugs possess high membrane permeability, their poor aqueous solubility significantly restricts the amount of drug available for absorption (Amidon et al., 1995). Consequently, dissolution becomes the rate-limiting step in oral drug absorption.

The low aqueous solubility of BCS Class-II antidiabetic drugs is primarily attributed to their physicochemical properties, including high lipophilicity, strong crystal lattice energy, low wettability, and tendency to aggregate in aqueous media (Kalepu & Nekkanti, 2015). Drugs such as glibenclamide, glimepiride, pioglitazone, and repaglinide possess hydrophobic molecular structures that limit their interaction with water molecules, resulting in poor dissolution behavior.

Crystalline Structure

The crystalline nature of drug substances is one of the most important factors influencing aqueous solubility. In crystalline materials, drug molecules are arranged in highly ordered lattices stabilized by intermolecular forces such as hydrogen bonding, van der Waals interactions, and electrostatic forces (Hancock & Parks, 2000).

A large amount of energy is required to break these interactions during dissolution. Consequently, highly crystalline drugs exhibit lower apparent solubility compared with amorphous forms. Most commercially available BCS Class-II antidiabetic drugs are manufactured in crystalline forms because of their superior physical stability. However, this stability often comes at the expense of reduced solubility and slower dissolution rates.

Polymorphism further complicates the situation. Different crystal forms may exhibit different lattice energies and consequently different dissolution characteristics. Less stable polymorphs generally possess higher solubility than thermodynamically stable crystal forms (Brittain, 2009).

Hydrophobicity

Hydrophobicity is commonly expressed using the partition coefficient (Log P), which reflects the affinity of a compound for lipid versus aqueous environments. BCS Class-II drugs generally exhibit moderate to high Log P values, indicating strong lipophilic characteristics (Savjani et al., 2012).

Although lipophilicity facilitates membrane permeation, excessive hydrophobicity decreases interaction with aqueous gastrointestinal fluids. As a result, drug particles remain poorly wetted and dissolve slowly. For example, glibenclamide possesses a Log P value of approximately 4.8, contributing to its extremely poor water solubility.

Particle Aggregation

Another factor limiting solubility is particle aggregation. Fine drug particles possess high surface free energy and tend to aggregate to minimize their total surface area. Aggregation reduces the effective surface area exposed to dissolution media, thereby decreasing dissolution rate and drug absorption (Danaei et al., 2018).

Poor wettability further exacerbates aggregation, particularly in hydrophobic drugs. Consequently, surfactants and wetting agents are frequently incorporated into formulations to improve particle dispersion and enhance dissolution.

Table 9: Drug-Related Factors Affecting Solubility

Factor	Mechanism	Impact on Bioavailability
Crystallinity	Strong lattice energy	Reduced dissolution
Hydrophobicity	Poor wettability	Slow dissolution
Aggregation	Reduced surface area	Low absorption
Large Particle Size	Lower surface exposure	Reduced dissolution

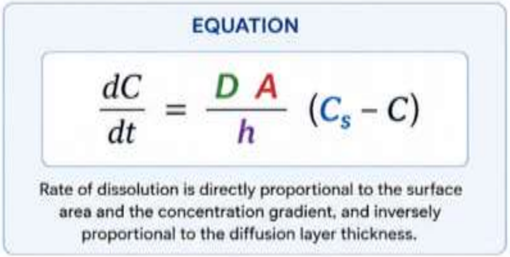
3.2 Dissolution Rate Limitations

For BCS Class-II drugs, dissolution is the primary determinant of oral absorption. The dissolution process controls the availability of drug molecules for permeation across the intestinal membrane.

Noyes–Whitney Equation

The dissolution behavior of poorly soluble drugs is commonly described by the Noyes–Whitney equation (Noyes & Whitney, 1897):

Equation 1: Noyes–Whitney Equation



EQUATION

$$\frac{dC}{dt} = \frac{D\,A}{h}(C_s - C)$$

Rate of dissolution is directly proportional to the surface area and the concentration gradient, and inversely proportional to the diffusion layer thickness.

Where:

- dC/dt = dissolution rate
- D = diffusion coefficient
- A = surface area
- Cs = saturation solubility
- C = concentration in bulk solution
- h = diffusion layer thickness

The equation demonstrates that dissolution rate can be enhanced by:

- Increasing surface area
- Increasing saturation solubility
- Decreasing diffusion layer thickness

This equation forms the theoretical basis for many formulation strategies such as particle size reduction, solid dispersions, nanoemulsions, and nanosuspensions.

Surface Area Effect

Particle size has a direct influence on dissolution behavior. Reduction in particle size increases surface area available for interaction with dissolution media (Kawabata et al., 2011).

Micronization and nanonization technologies exploit this principle to improve dissolution rates. Nanocrystals, in particular, provide enormous surface area, resulting in significantly enhanced dissolution and absorption.

Table 10: Variables Affecting Dissolution Rate According to Noyes–Whitney Equation

Parameter	Effect on Dissolution
Surface Area (A) ↑	Dissolution Increases
Saturation Solubility (Cs) ↑	Dissolution Increases
Diffusion Layer Thickness (h) ↓	Dissolution Increases
Diffusion Coefficient (D) ↑	Dissolution Increases

3.3 Gastrointestinal Factors

In addition to drug properties, gastrointestinal physiology plays a crucial role in determining oral bioavailability.

pH Variations

The pH of the gastrointestinal tract varies considerably, ranging from approximately 1–3 in the stomach to 6–8 in the intestine. Changes in pH influence drug ionization, solubility, and dissolution behavior (Dressman & Reppas, 2020).

Weakly acidic drugs such as glibenclamide often exhibit poor solubility under gastric conditions but improved dissolution in intestinal fluids. Conversely, pH-dependent precipitation may occur upon transit between different gastrointestinal compartments.

Gastric Emptying

Gastric emptying determines the residence time of drugs within the stomach. Delayed gastric emptying may prolong exposure to acidic conditions and affect dissolution patterns (Shargel & Yu, 2016).

Food intake, disease states, and patient variability can significantly influence gastric emptying rates and ultimately drug absorption.

Intestinal Transit Time

Intestinal transit time determines the duration available for drug absorption. Rapid transit may limit dissolution and reduce absorption of poorly soluble drugs, whereas prolonged residence time may improve bioavailability (Dressman & Reppas, 2020).

Table 11: Gastrointestinal Factors Influencing BCS Class-II Drug Absorption

Factor	Influence on Absorption
Gastric pH	Alters ionization
Intestinal pH	Influences dissolution
Gastric Emptying	Changes residence time
Transit Time	Alters absorption window
Food Intake	Affects solubilization

3.4 Drug–Excipient Interactions

Excipients play a critical role in formulation development and may significantly influence drug dissolution, stability, and bioavailability.

Influence on Dissolution

Hydrophilic carriers such as polyethylene glycol (PEG), polyvinylpyrrolidone (PVP), hydroxypropyl methylcellulose (HPMC), and Soluplus® improve wettability and dissolution of poorly soluble drugs (Kalepu & Nekkanti, 2015).

Surfactants such as Tween 80, Cremophor EL, and Poloxamers reduce interfacial tension and facilitate drug solubilization.

Stability Concerns

Although excipients can improve dissolution, they may also influence drug stability. Potential concerns include:

- Drug recrystallization
- Chemical degradation

- Moisture absorption
- Drug-excipient incompatibility

Therefore, compatibility studies are essential during formulation development.

Table 12: Common Excipients Used for Solubility Enhancement

Excipient	Function	Example Application
PEG	Hydrophilic carrier	Solid dispersions
PVP	Amorphous stabilization	Solid dispersions
HPMC	Dissolution enhancement	Tablets
Soluplus®	Polymeric solubilizer	Amorphous dispersions
Tween 80	Surfactant	Nanoemulsions
Poloxamer 188	Wetting agent	Nanosuspensions

4. CONVENTIONAL FORMULATION APPROACHES

4.1 Particle Size Reduction

Particle size reduction is one of the oldest and most widely employed approaches for enhancing the dissolution rate and oral bioavailability of poorly water-soluble drugs. According to the Noyes–Whitney equation, dissolution rate is directly proportional to the surface area available for dissolution (Noyes & Whitney, 1897). Therefore, reducing particle size increases the surface area-to-volume ratio, leading to improved wettability and dissolution.

For BCS Class-II antidiabetic drugs such as glibenclamide, glimepiride, pioglitazone, and repaglinide, particle size reduction has been extensively investigated as a means of overcoming dissolution-limited absorption (Kawabata et al., 2011).

Micronization

Micronization refers to the reduction of particle size into the micrometer range (typically 1–10 µm). The process is commonly performed using jet milling, ball milling, hammer milling, or fluid energy milling techniques (Savjani et al., 2012).

Principle

Micronization increases the surface area exposed to dissolution media, thereby accelerating drug dissolution and improving oral absorption.

Advantages

- Simple and cost-effective process
- Applicable to a wide range of drugs
- Easily scalable for industrial production
- Improves dissolution rate without altering chemical structure

Limitations

- Does not alter intrinsic solubility
- High-energy processes may induce crystal defects
- Fine particles tend to aggregate
- Limited improvement for extremely hydrophobic drugs

Studies on micronized glibenclamide formulations have demonstrated enhanced dissolution rates and improved hypoglycemic activity compared with conventional formulations (Sweetman, 2020).

Nanonization

Nanonization reduces drug particles into the nanometer range (10–1000 nm), providing a significantly larger surface area than micronized particles (Müller & Keck, 2004).

Wet Milling

Wet milling involves the mechanical reduction of particle size in the presence of stabilizers and aqueous media. The technique produces stable nanosuspensions suitable for oral delivery.

High-Pressure Homogenization

High-pressure homogenization forces drug suspensions through narrow gaps at high pressure, generating intense shear forces that reduce particle size.

Drug Nanocrystals

Drug nanocrystals consist of pure drug particles stabilized by surfactants or polymers. Their increased surface area and enhanced saturation solubility result in superior dissolution characteristics (Müller & Keck, 2004).

Several studies have reported significant enhancement in the dissolution and bioavailability of glimepiride and pioglitazone nanocrystals compared with their coarse counterparts.

Applications in Antidiabetic Drugs

Particle size reduction has been successfully applied to:

- Glibenclamide nanocrystals
- Glimepiride nanosuspensions
- Pioglitazone nanoparticles
- Repaglinide nanocrystals

These systems have shown improved dissolution profiles, faster onset of action, and enhanced oral bioavailability.

Table 13:Comparison of Micronization and Nanonization

Parameter	Micronization	Nanonization
Particle Size	1–10 µm	10–1000 nm
Surface Area	Moderate	Very High
Dissolution Enhancement	Moderate	High
Bioavailability Improvement	Moderate	High
Cost	Low	Higher

4.2 Solid Dispersion Technology

Solid dispersion technology is among the most effective approaches for improving the dissolution behavior of poorly soluble drugs. The technique involves dispersing a hydrophobic drug within a hydrophilic carrier matrix to improve wettability, reduce crystallinity, and enhance apparent solubility (Chiou & Riegelman, 1971).

Principle

When dispersed at the molecular or amorphous level within a carrier, the drug exhibits:

- Improved wettability
- Reduced particle size
- Increased surface area
- Enhanced dissolution rate

Types of Solid Dispersions

Eutectic Systems

Drug and carrier crystallize separately but in finely divided forms.

Solid Solutions

Drug molecules are molecularly dispersed within the carrier matrix.

Amorphous Solid Dispersions

Drug exists in an amorphous state, exhibiting higher apparent solubility than crystalline forms (Hancock & Parks, 2000).

Carriers Used

Polyethylene Glycol (PEG)

- Hydrophilic polymer
- Improves wettability
- Commonly used in melt-based dispersions

Polyvinylpyrrolidone (PVP)

- Excellent amorphous stabilizer
- Enhances dissolution

Hydroxypropyl Methylcellulose (HPMC)

- Maintains supersaturation
- Prevents recrystallization

Soluplus®

- Amphiphilic polymer
- Particularly useful for BCS Class-II drugs

Applications in Glibenclamide and Glimepiride

Solid dispersions of glibenclamide using PEG and PVP have demonstrated several-fold increases in dissolution rates. Similarly, glimepiride-Soluplus® dispersions have shown substantial improvements in bioavailability.

Mechanism of Solid Dispersion

Crystalline Drug
+
Hydrophilic Carrier
↓
Molecular Dispersion
↓
Improved Wettability
↓
Enhanced Dissolution

Table 14: Common Carriers Used in Solid Dispersion Systems

Carrier	Type	Function
PEG	Hydrophilic Polymer	Wettability enhancement
PVP	Amorphous Stabilizer	Dissolution enhancement
HPMC	Polymer	Recrystallization inhibition
Soluplus®	Amphiphilic Polymer	Solubilization

4.3 Crystal Engineering

Crystal engineering refers to the modification of crystal structure to improve physicochemical properties such as solubility, dissolution rate, and stability (Brittain, 2009).

Polymorphism

Polymorphism occurs when a drug exists in multiple crystalline forms.

Different polymorphs may exhibit:

- Different melting points
- Different lattice energies
- Different dissolution rates

Metastable polymorphs generally possess higher solubility than stable crystal forms.

Co-Crystals

Co-crystals consist of an active pharmaceutical ingredient and a co-former held together through non-covalent interactions.

Advantages include:

- Improved solubility
- Enhanced dissolution rate
- Better physical stability
- Improved manufacturability

Several glibenclamide and pioglitazone co-crystals have shown significantly improved dissolution profiles.

Amorphous Systems

Amorphous drugs lack long-range molecular order and possess higher free energy than crystalline forms (Hancock & Parks, 2000).

Advantages:

- Increased apparent solubility
- Rapid dissolution
- Improved bioavailability

However, physical instability and recrystallization remain major concerns.

Impact on Solubility

Crystal engineering modifies molecular packing and lattice energy, reducing the energy required for dissolution. Consequently, crystal-engineered systems frequently exhibit enhanced dissolution behavior and oral absorption.

Table 15: Crystal Engineering Strategies for BCS Class-II Drugs

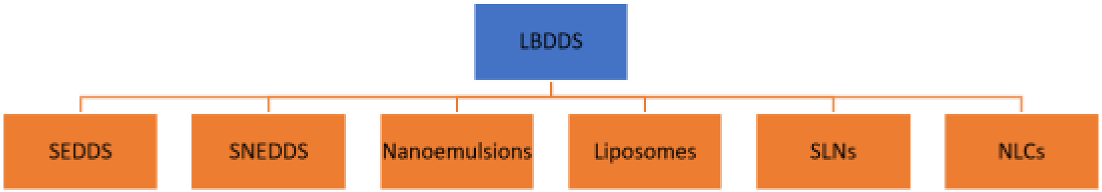
Strategy	Mechanism	Advantage	Limitation
Polymorphism	Crystal modification	Improved dissolution	Stability issues
Co-crystals	Molecular complexation	Improved solubility	Co-former selection
Amorphous Systems	Reduced crystallinity	High solubility	Recrystallization

5. LIPID-BASED DRUG DELIVERY SYSTEMS

Lipid-based drug delivery systems (LBDDS) have emerged as one of the most effective approaches for improving the oral bioavailability of poorly water-soluble drugs. These systems utilize lipids, surfactants, and co-surfactants to enhance drug solubilization, facilitate intestinal absorption, and reduce the impact of dissolution-limited absorption (Porter et al., 2007). The ability of lipid-based formulations to maintain drugs in a solubilized state throughout gastrointestinal transit makes them particularly attractive for BCS Class-II antidiabetic drugs such as glibenclamide, glimepiride, pioglitazone, and repaglinide.

The mechanisms by which lipid-based formulations enhance bioavailability include improved drug solubilization, increased surface area for absorption, stimulation of lymphatic transport, inhibition of efflux transporters, and protection against enzymatic degradation (Pouton, 2006). Consequently, numerous lipid-based systems have been developed, including self-emulsifying drug delivery systems (SEDDS), self-nanoemulsifying drug delivery systems (SNEDDS), nanoemulsions, liposomes, solid lipid nanoparticles (SLNs), and nanostructured lipid carriers (NLCs).

Classification of Lipid-Based Drug Delivery Systems



5.1 Self-Emulsifying Drug Delivery Systems (SEDDS)

Introduction and Principle

Self-emulsifying drug delivery systems (SEDDS) are isotropic mixtures of oils, surfactants, and co-solvents that spontaneously form fine oil-in-water emulsions upon dilution with gastrointestinal fluids under gentle agitation (Pouton, 2006).

The spontaneous emulsification process significantly increases the interfacial surface area available for drug release and absorption. Unlike conventional formulations, SEDDS maintain poorly soluble drugs in a dissolved state, thereby minimizing precipitation during gastrointestinal transit.

Components of SEDDS

Oils

The oil phase serves as the primary solubilization medium for lipophilic drugs.

Common oils include:

- Capryol® 90
- Oleic acid
- Medium-chain triglycerides (MCT)
- Long-chain triglycerides (LCT)

Surfactants

Surfactants reduce interfacial tension and facilitate self-emulsification.

Common surfactants include:

- Tween 80
- Cremophor RH40
- Labrasol®
- Kolliphor EL

Co-Surfactants

Co-surfactants improve flexibility of the interfacial film and facilitate nano-droplet formation.

Examples include:

- Transcutol® P
- PEG 400
- Propylene glycol
- Ethanol

Advantages of SEDDS

- Improved solubility of hydrophobic drugs
- Enhanced oral bioavailability
- Reduced food effect

- Ease of manufacturing
- Improved dose uniformity

Applications in Antidiabetic Drugs

SEDDS formulations of glibenclamide and repaglinide have demonstrated significant improvements in dissolution rate and oral bioavailability compared with conventional tablets (Patel et al., 2020).

Mechanism of Self-Emulsification

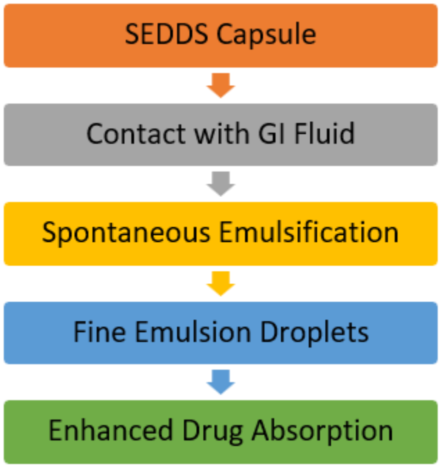


Table 16: Common Components Used in SEDDS Formulations

Component Type	Examples	Function
Oils	Capryol®, Oleic Acid	Drug Solubilization
Surfactants	Tween 80, Cremophor RH40	Emulsification
Co-Surfactants	PEG 400, Transcutol P	Interfacial Stabilization

5.2 Self-Nanoemulsifying Drug Delivery Systems (SNEDDS)

Formulation Design

SNEDDS are advanced versions of SEDDS that produce nano-sized emulsions with droplet diameters generally below 200 nm upon dilution (Porter et al., 2007).

The formulation design process typically involves:

1. Solubility screening
2. Selection of oil phase
3. Surfactant screening
4. Construction of pseudo-ternary phase diagrams
5. Optimization using Design of Experiments (DoE)

Mechanism of Bioavailability Enhancement

SNEDDS improve bioavailability through:

- Increased dissolution rate
- Improved intestinal permeability
- Enhanced lymphatic transport
- Reduced first-pass metabolism
- Improved drug stability

Recent Research Findings

Several studies have demonstrated:

- 2–6 fold improvement in glibenclamide bioavailability
- Enhanced dissolution of glimepiride
- Increased oral absorption of pioglitazone

Table 17: Recent SNEDDS Formulations for Antidiabetic Drugs

Drug	Oil	Surfactant	Outcome
Glibenclamide	Capryol®	Tween 80	Enhanced Bioavailability
Pioglitazone	Oleic Acid	Cremophor RH40	Improved Dissolution
Glimepiride	MCT Oil	Labrasol®	Faster Absorption

5.3 Nanoemulsions

Introduction

Nanoemulsions are thermodynamically or kinetically stable colloidal dispersions consisting of oil droplets dispersed in an aqueous phase with droplet sizes typically ranging from 20–200 nm (McClements, 2012).

Nanoemulsions offer several advantages:

- High drug loading capacity
- Enhanced solubilization
- Improved stability
- Increased absorption surface area

Components

Oil Phase

- Oleic acid
- Capryol® 90
- Isopropyl myristate
- Medium-chain triglycerides

Surfactant

- Tween 80
- Cremophor EL
- Labrasol®

Co-Surfactant

- PEG 400
- Transcutol P
- Ethanol

Aqueous Phase

- Purified water
- Buffer systems

Preparation Methods

High-Energy Methods

- High-pressure homogenization
- Ultrasonication
- Microfluidization

Low-Energy Methods

- Phase inversion temperature method
- Spontaneous emulsification

Characterization

Key characterization parameters include:

- Droplet size
- Polydispersity index (PDI)
- Zeta potential
- Drug loading

- Entrapment efficiency
- In vitro drug release

Applications in Glibenclamide and Pioglitazone

Nanoemulsions have demonstrated:

- Enhanced dissolution rates
- Increased intestinal absorption
- Improved glycemic control
- Reduced dose requirements

Structure of a Nanoemulsion

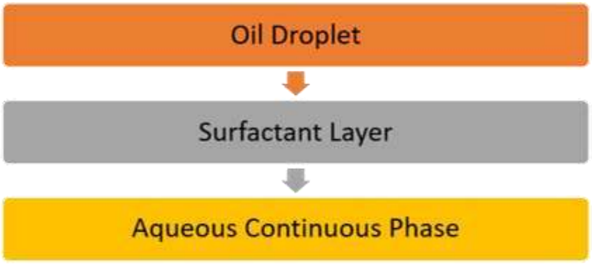


Table 18: Nanoemulsion Formulations Reported for Antidiabetic Drugs

Drug	Oil Phase	Droplet Size (nm)	Bioavailability Enhancement
Glibenclamide	Capryol®	90–150	3–5 Fold
Pioglitazone	Oleic Acid	80–120	2–4 Fold
Glimepiride	IPM	70–130	3 Fold

5.4 Liposomes

Structure

Liposomes are vesicular systems composed of phospholipid bilayers surrounding aqueous compartments (Akbarzadeh et al., 2013).

Preparation Techniques

- Thin-film hydration
- Reverse-phase evaporation
- Ethanol injection
- Sonication

Advantages

- Biocompatibility
- Controlled release
- Reduced toxicity
- Enhanced drug stability

Antidiabetic Applications

Liposomal formulations of pioglitazone have demonstrated improved pharmacokinetic profiles and reduced systemic toxicity.

Liposome Structure

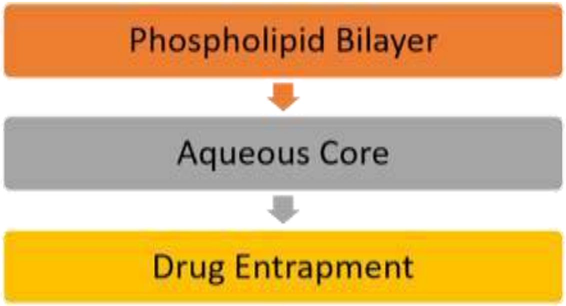


Table 19: Advantages and Limitations of Liposomes

Advantages	Limitations
Biocompatible	High Cost
Controlled Release	Stability Issues
Enhanced Absorption	Scale-Up Challenges

5.5 Solid Lipid Nanoparticles (SLNs)

Composition

SLNs consist of:

- Solid lipid matrix
- Surfactant
- Stabilizer

Advantages

- Controlled release
- Enhanced stability
- Protection of drug molecules
- Improved bioavailability

Recent Developments

SLN formulations of glibenclamide and pioglitazone have shown enhanced oral absorption and prolonged therapeutic effects.

Structure of Solid Lipid Nanoparticles

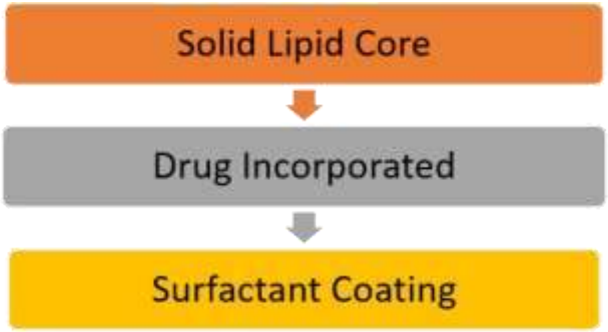


Table 20: SLN-Based Antidiabetic Formulations

Drug	Lipid Used	Outcome
Glibenclamide	Glyceryl Monostearate	Improved Bioavailability
Pioglitazone	Stearic Acid	Sustained Release

5.6 Nanostructured Lipid Carriers (NLCs)

Formulation

NLCs are second-generation lipid nanoparticles consisting of a mixture of solid and liquid lipids (Müller et al., 2002).

Advantages Over SLNs

- Higher drug loading
- Reduced drug expulsion
- Better long-term stability
- Improved release characteristics

Therapeutic Applications

NLC formulations of antidiabetic drugs have demonstrated:

- Enhanced oral absorption
- Sustained release
- Improved glycemic control
- Reduced dosing frequency

Table 21: Comparison of SLNs and NLCs

Parameter	SLNs	NLCs
Drug Loading	Moderate	High
Stability	Good	Excellent
Drug Expulsion	Possible	Reduced
Bioavailability	High	Very High

6. POLYMERIC NANOCARRIER SYSTEMS

Polymeric nanocarriers have emerged as highly promising drug delivery platforms for improving the oral bioavailability of BCS Class-II antidiabetic drugs. These systems offer several advantages, including enhanced solubility, controlled drug release, protection from degradation, prolonged circulation time, and targeted drug delivery. Polymeric nanocarriers can encapsulate hydrophobic drugs within their matrix or core, thereby improving dissolution and absorption characteristics (Danhier et al., 2012).

For poorly water-soluble antidiabetic drugs such as glibenclamide, glimepiride, pioglitazone, and repaglinide, polymeric nanocarriers have demonstrated significant improvements in bioavailability and therapeutic efficacy. The major polymeric nanocarrier systems include polymeric nanoparticles, polymeric micelles, dendrimers, hydrogels, and nanogels.

6.1 Polymeric Nanoparticles

Polymeric nanoparticles are colloidal systems typically ranging from 10–1000 nm in size, composed of biodegradable and biocompatible polymers. Depending on their structure, polymeric nanoparticles may be classified as nanospheres or nanocapsules (Danhier et al., 2012).

Mechanism of Bioavailability Enhancement

Polymeric nanoparticles improve oral bioavailability through:

- Enhanced solubilization of hydrophobic drugs
- Increased surface area
- Improved mucoadhesion
- Protection against enzymatic degradation
- Controlled drug release
- Enhanced cellular uptake

Natural Polymers

Natural polymers possess excellent biocompatibility and low toxicity.

Chitosan

Chitosan is a cationic polysaccharide obtained from chitin. It exhibits:

- Mucoadhesive properties
- Permeation-enhancing effects
- Biodegradability
- Controlled release characteristics

Chitosan nanoparticles have been extensively investigated for oral delivery of glibenclamide and pioglitazone, showing improved absorption and prolonged hypoglycemic effects (Agnihotri et al., 2004).

Alginate

Alginate is an anionic polysaccharide derived from brown seaweed.

Advantages include:

- Biocompatibility
- pH-responsive behavior
- Mild gelation conditions
- Sustained drug release

Alginate-based nanoparticles have shown potential in improving oral delivery of antidiabetic drugs.

Synthetic Polymers

Synthetic polymers offer greater control over physicochemical properties and degradation kinetics.

Poly(lactic-co-glycolic acid) (PLGA)

PLGA is one of the most extensively studied biodegradable polymers approved by regulatory agencies.

Advantages:

- Excellent biocompatibility
- Controlled release capability
- Adjustable degradation rate
- High drug encapsulation efficiency

PLGA nanoparticles have been successfully employed for pioglitazone and glimepiride delivery (Makadia & Siegel, 2011).

Polycaprolactone (PCL)

PCL is a semi-crystalline biodegradable polymer characterized by:

- Slow degradation rate
- High stability
- Sustained release capability

PCL nanoparticles have shown promising results for long-term antidiabetic therapy.

Classification of Polymeric Nanoparticles

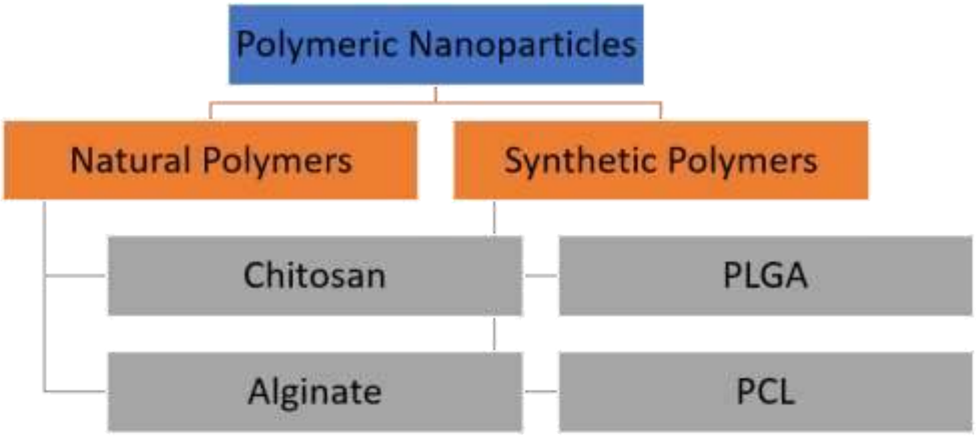


Table 22: Natural and Synthetic Polymers Used in Antidiabetic Drug Delivery

Polymer	Type	Advantages	Applications
Chitosan	Natural	Mucoadhesive	Glibenclamide
Alginate	Natural	pH-sensitive	Oral delivery
PLGA	Synthetic	Controlled release	Pioglitazone
PCL	Synthetic	Long-term release	Sustained therapy

6.2 Polymeric Micelles

Polymeric micelles are self-assembled nanostructures formed from amphiphilic block copolymers in aqueous environments. They typically possess sizes ranging from 10–100 nm (Torchilin, 2007).

Structure

Polymeric micelles consist of:

- Hydrophobic core
- Hydrophilic shell

The hydrophobic core acts as a reservoir for poorly soluble drugs, while the hydrophilic shell stabilizes the system in biological fluids.

Drug Loading

Hydrophobic antidiabetic drugs are incorporated into the micellar core through:

- Hydrophobic interactions
- Van der Waals forces
- Hydrogen bonding

Solubilization Mechanism

Micelles significantly enhance apparent solubility by maintaining drug molecules within the hydrophobic core in a dissolved state.

Advantages include:

- High solubilization efficiency
- Small particle size
- Enhanced permeability
- Improved stability

Table 23: Characteristics of Polymeric Micelles

Parameter	Description
Size Range	10–100 nm
Core	Hydrophobic
Shell	Hydrophilic
Drug Loading	High
Solubility Enhancement	Excellent

6.3 Dendrimers

Dendrimers are highly branched, monodisperse macromolecules characterized by a tree-like architecture. Their unique structure provides multiple functional groups for drug loading and surface modification (Tomalia et al., 2005).

Classification

Dendrimers are classified according to generation number:

- G0 (Core)
- G1–G10 (Higher generations)

Higher generations possess:

- Increased surface functionality
- Larger internal cavities
- Greater drug-loading capacity

Drug Encapsulation

Drugs may be incorporated through:

- Physical entrapment
- Electrostatic interactions
- Covalent conjugation

Advantages

- High loading capacity
- Controlled release
- Enhanced solubility
- Targeted delivery capability

Dendrimer-based systems have demonstrated improved solubilization of several hydrophobic antidiabetic drugs.

Limitations of Dendrimers

- Expensive
- Complex Synthesis

- Potential Toxicity
- Scale-up Challenges

6.4 Hydrogels and Nanogels

Hydrogels are three-dimensional polymeric networks capable of absorbing large quantities of water while maintaining structural integrity (Peppas et al., 2000).

Nanogels are nanosized hydrogel particles that combine hydrogel properties with nanotechnology-based advantages.

Preparation

Common preparation methods include:

- Chemical crosslinking
- Physical crosslinking
- Emulsion polymerization
- Radiation-induced polymerization

Controlled Release Potential

Hydrogels and nanogels offer:

- Sustained release
- Stimuli-responsive behavior
- Improved patient compliance
- Enhanced drug stability

Applications in Antidiabetic Therapy

Hydrogel systems have been investigated for:

- Oral delivery of glibenclamide
- Controlled release of pioglitazone
- Glucose-responsive drug delivery

Stimuli-Responsive Hydrogels

Advanced hydrogels respond to:

- pH
- Temperature
- Glucose concentration
- Enzymatic activity

These smart systems may facilitate personalized diabetes management in the future.

Comparative Analysis of Polymeric Nanocarriers

Table 24: Comparison of Polymeric Nanocarrier Systems

System	Size Range	Drug Loading	Release Control	Bioavailability Enhancement
Polymeric Nanoparticles	50–1000 nm	High	Excellent	High
Polymeric Micelles	10–100 nm	Moderate–High	Moderate	Very High
Dendrimers	5–20 nm	Very High	Excellent	High
Hydrogels	Variable	Moderate	Excellent	Moderate
Nanogels	20–200 nm	High	Excellent	High

7. ADVANCED DRUG DELIVERY SYSTEMS

Advanced drug delivery systems have gained considerable attention for overcoming the solubility and bioavailability limitations associated with BCS Class-II antidiabetic drugs.

While conventional and lipid-based formulations improve dissolution and absorption, advanced delivery systems provide additional advantages such as controlled release, targeted delivery, enhanced stability, improved mucoadhesion, and prolonged therapeutic action. Among these technologies, nanosuspensions, inclusion complexes, mesoporous silica nanoparticles, and mucoadhesive systems have demonstrated significant potential for improving the oral delivery of poorly soluble antidiabetic drugs such as glibenclamide, glimepiride, pioglitazone, and repaglinide.

7.1 Nanosuspensions

Introduction

Nanosuspensions are submicron colloidal dispersions of pure drug particles stabilized by surfactants or polymers. The particle size typically ranges from 100–1000 nm, resulting in a dramatic increase in surface area and dissolution rate (Müller & Keck, 2004).

Unlike lipid-based systems, nanosuspensions contain minimal excipients and are particularly suitable for drugs with poor solubility in both aqueous and lipid media.

Preparation Methods

Top-Down Technologies

Top-down approaches reduce the size of larger drug particles through mechanical processes.

Wet Media Milling

Drug particles are milled in the presence of stabilizers using grinding media.

Advantages:

- Industrial scalability
- Uniform particle size
- High drug loading

High-Pressure Homogenization

Drug suspensions are forced through narrow gaps under high pressure.

Advantages:

- Solvent-free process
- Reproducibility
- Large-scale manufacturing

Bottom-Up Technologies

Bottom-up approaches involve precipitation of drug molecules from solution.

Solvent–Antisolvent Precipitation

Drug dissolved in solvent
↓
Addition to antisolvent
↓
Rapid nucleation
↓
Nanoparticle formation

Advantages

- Increased dissolution rate
- Improved saturation solubility
- Enhanced bioavailability
- Reduced food effect
- Simple formulation composition

Applications in Antidiabetic Drugs

Studies have reported:

- Glibenclamide nanosuspensions showing 3–5 fold dissolution enhancement.

- Pioglitazone nanosuspensions improving oral absorption.

- Glimepiride nanocrystals demonstrating faster onset of action.

Table 25: Nanosuspension Technologies

Method	Principle	Advantages	Limitations
Wet Milling	Particle size reduction	Scalable	Equipment wear
High-Pressure Homogenization	Shear force generation	Uniform particles	High energy requirement
Precipitation	Controlled nucleation	Small particles	Solvent removal required

7.2 Inclusion Complexes

Introduction

Inclusion complexation is a molecular encapsulation technique used to improve the solubility, dissolution rate, and stability of poorly soluble drugs. The most commonly used complexing agents are cyclodextrins (Loftsson & Brewster, 2010).

Cyclodextrins possess:

- Hydrophilic outer surface

- Hydrophobic inner cavity

This unique structure allows hydrophobic drug molecules to be accommodated within the cavity while maintaining aqueous solubility.

Cyclodextrin-Based Complexes

Common cyclodextrins include:

- α-Cyclodextrin

- β-Cyclodextrin

- γ-Cyclodextrin

- Hydroxypropyl-β-cyclodextrin (HPβCD)

Solubility Enhancement Mechanism

Poorly Soluble Drug
↓
Inclusion into Cyclodextrin Cavity
↓
Improved Aqueous Solubility
↓
Enhanced Dissolution
↓
Improved Absorption

Applications in Antidiabetic Drugs

Cyclodextrin complexes have been reported for:

- Glibenclamide

- Pioglitazone

- Repaglinide

- Glimepiride

These complexes significantly improve dissolution and oral bioavailability.

Table 26: Cyclodextrins Used for Solubility Enhancement

Cyclodextrin	Characteristics	Pharmaceutical Application
α-CD	Small cavity	Small molecules
β-CD	Most common	Solubility enhancement
γ-CD	Large cavity	Large molecules

HPβCD	Highly water soluble	Oral formulations

7.3 Mesoporous Silica Nanoparticles (MSNs)

Introduction

Mesoporous silica nanoparticles are inorganic nanocarriers characterized by highly ordered pore structures and large surface areas (Vallet-Regí et al., 2007).

Typical properties include:

- Surface area >700 m²/g
- Pore size 2–50 nm
- High drug-loading capacity
- Tunable surface chemistry

Drug Loading

Drug molecules are loaded into nanopores through:

- Adsorption
- Solvent evaporation
- Impregnation methods

The confined environment inside pores often converts crystalline drugs into amorphous forms, significantly improving dissolution behavior.

Controlled Release Mechanism

MSNs can provide:

- Sustained release
- Stimuli-responsive release
- Targeted delivery

Applications in Antidiabetic Drugs

Research has demonstrated enhanced dissolution of:

- Glibenclamide
- Glimepiride
- Pioglitazone

through incorporation into mesoporous silica matrices.

Mesoporous Silica Nanoparticle Structure

Porous Silica Matrix
↓
Drug Loaded Nanopores
↓
Controlled Drug Release

Table 27: Advantages of Mesoporous Silica Nanoparticles

Property	Benefit
Large Surface Area	High drug loading
Mesoporous Structure	Enhanced dissolution
Surface Functionalization	Targeting capability
Physical Stability	Improved shelf life

7.4 Mucoadhesive Systems

Introduction

Mucoadhesive systems are designed to adhere to the mucus layer covering gastrointestinal tissues, thereby prolonging residence time and improving drug absorption (Andrews et al., 2009).

For BCS Class-II antidiabetic drugs, extended residence time can significantly enhance dissolution and absorption.

Mechanism of Mucoadhesion

The mucoadhesion process involves:

Stage 1: Contact

Drug delivery system comes into contact with mucus layer.

Stage 2: Interpenetration

Polymer chains interpenetrate mucus glycoproteins.

Stage 3: Adhesion

Hydrogen bonding and electrostatic interactions establish strong attachment.

Common Mucoadhesive Polymers

Natural Polymers

- Chitosan
- Alginate
- Pectin

Synthetic Polymers

- Carbopol
- Polycarbophil
- HPMC

Bioavailability Benefits

Mucoadhesive systems improve:

- Gastrointestinal residence time
- Drug dissolution
- Local drug concentration
- Intestinal permeability

Applications in Antidiabetic Drug Delivery

Mucoadhesive formulations of glibenclamide and pioglitazone have shown:

- Enhanced absorption
- Sustained release
- Improved glycemic control

Mechanism of Mucoadhesion

Drug Carrier
↓
Contact with Mucus
↓
Polymer-Mucin Interaction
↓
Adhesion
↓
Enhanced Drug Absorption

Table 28: Mucoadhesive Polymers Used in Oral Drug Delivery

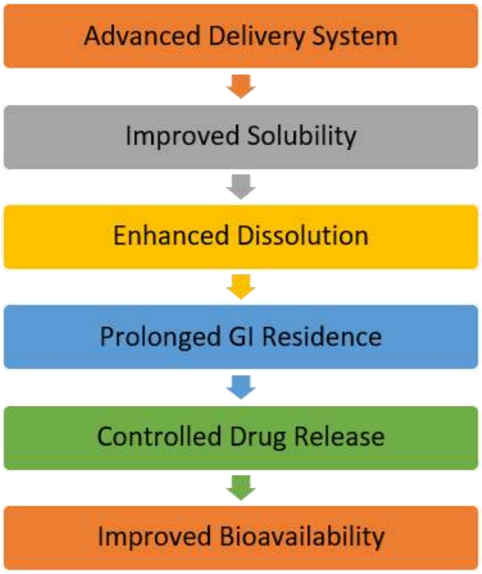
Polymer	Type	Function
Chitosan	Natural	Permeation enhancer
Alginate	Natural	Sustained release
Carbopol	Synthetic	Strong adhesion
HPMC	Synthetic	Controlled release

Comparative Analysis of Advanced Drug Delivery Systems

Table 29: Comparison of Advanced Drug Delivery Systems for BCS Class-II Drugs

System	Solubility Enhancement	Drug Loading	Controlled Release	Scale-Up Potential
Nanosuspension	High	Excellent	Moderate	High
Inclusion Complex	Moderate–High	Moderate	Low	Excellent
Mesoporous Silica Nanoparticles	High	High	High	Moderate
Mucoadhesive Systems	Moderate	Moderate	High	High

Mechanisms of Bioavailability Enhancement in Advanced Drug Delivery Systems



8. COMPARATIVE ANALYSIS OF FORMULATION STRATEGIES

8.1 Comparative Evaluation of Solubility Enhancement Strategies

The primary objective of formulation development for BCS Class-II drugs is to improve aqueous solubility and dissolution rate. Different technologies achieve this goal through distinct mechanisms.

Conventional Approaches

Micronization, nanonization, solid dispersions, and crystal engineering primarily improve dissolution by increasing surface area or reducing crystallinity (Kawabata et al., 2011).

Advantages:

- Simpler manufacturing
- Lower production costs
- Established regulatory acceptance

Limitations:

- Limited drug loading
- Physical instability
- Recrystallization risks

Lipid-Based Systems

Lipid-based formulations improve drug solubilization through incorporation within lipid matrices and emulsified systems.

Advantages:

- Excellent solubilization capacity
- Lymphatic transport enhancement
- Reduced food effect

Limitations:

- Surfactant-associated toxicity
- Stability concerns
- Formulation complexity

Polymeric Nanocarriers

Polymeric systems improve bioavailability through encapsulation, controlled release, and enhanced mucosal interaction.

Advantages:

- Controlled release
- High encapsulation efficiency
- Improved stability

Limitations:

- Complex manufacturing

- Higher cost

Advanced Drug Delivery Systems

Technologies such as nanosuspensions, inclusion complexes, and mesoporous silica nanoparticles provide additional flexibility for enhancing dissolution and drug release characteristics.

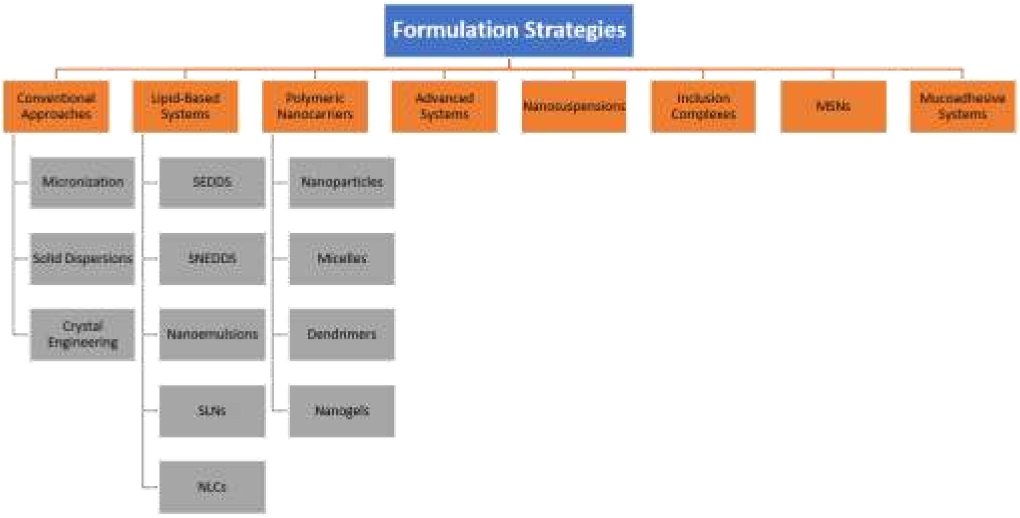
Advantages:

- High drug loading
- Versatile formulation design

Limitations:

- Scale-up challenges
- Regulatory complexities

Classification of Formulation Strategies for BCS Class-II Drugs



8.2 Comparative Analysis of Solubility Enhancement

The magnitude of solubility enhancement varies among formulation strategies.

Solid dispersions generally improve dissolution by converting crystalline drugs into amorphous forms. Nanoemulsions and SNEDDS often provide greater solubilization due to the presence of lipidic solubilization reservoirs (Porter et al., 2007).

NLCs frequently demonstrate superior drug loading and long-term stability compared with SLNs because of their imperfect lipid matrices.

Polymeric micelles and dendrimers exhibit exceptional solubilization capacity for highly lipophilic compounds but may be associated with manufacturing complexity.

Table 30: Comparison of Solubility Enhancement Potential

Technology	Solubility Enhancement	Mechanism
Micronization	Moderate	Surface area increase
Nanocrystals	High	Surface area increase
Solid Dispersion	High	Amorphization

SEDDS	Very High	Self-emulsification
SNEDDS	Very High	Nanoemulsification
Nanoemulsion	Very High	Drug solubilization
SLNs	High	Lipid encapsulation
NLCs	Very High	Imperfect lipid matrix
Polymeric Micelles	Very High	Core encapsulation
Inclusion Complexes	Moderate–High	Molecular complexation

8.3 Stability Considerations

Formulation stability is critical for commercial success.

Physical Stability

Challenges include:

- Particle aggregation
- Drug precipitation
- Phase separation
- Recrystallization

Nanoemulsions and SNEDDS generally exhibit excellent thermodynamic stability, while solid dispersions may experience recrystallization during storage (Hancock & Parks, 2000).

Chemical Stability

Factors affecting chemical stability include:

- Oxidation
- Hydrolysis
- Polymer degradation
- Lipid degradation

Polymeric nanoparticles and NLCs often provide superior protection against degradation.

8.4 Scale-Up and Manufacturing Considerations

Commercial translation requires scalable and reproducible manufacturing processes.

High Scale-Up Potential

- Micronization
- Solid dispersions
- SEDDS
- SNEDDS

These technologies are already utilized in several marketed pharmaceutical products.

Moderate Scale-Up Potential

- Nanoemulsions
- SLNs
- NLCs
- Polymeric nanoparticles

Scale-up may require specialized equipment and process optimization.

Low-to-Moderate Scale-Up Potential

- Dendrimers
- Mesoporous silica nanoparticles
- Stimuli-responsive nanogels

Manufacturing complexity remains a major challenge.

Table 31: Manufacturing and Scale-Up Comparison

Technology	Manufacturing Complexity	Scale-Up Potential
Micronization	Low	Excellent
Solid Dispersion	Low–Moderate	Excellent
SEDDS	Moderate	Excellent
SNEDDS	Moderate	Excellent
Nanoemulsion	Moderate	Good
SLNs	Moderate–High	Good
NLCs	Moderate–High	Good
Polymeric Nanoparticles	High	Moderate
Dendrimers	Very High	Limited

8.5 Suitability for Antidiabetic Drugs

The selection of formulation strategy depends on the physicochemical characteristics of individual antidiabetic drugs.

Glibenclamide

Most suitable systems:

- Nanoemulsions
- SNEDDS
- NLCs
- Solid dispersions

Glimepiride

Most suitable systems:

- Nanocrystals
- Polymeric nanoparticles
- Nanoemulsions

Pioglitazone

Most suitable systems:

- Nanoemulsions
- NLCs
- Polymeric micelles

Repaglinide

Most suitable systems:

- SEDDS
- SNEDDS
- Inclusion complexes

8.6 Decision-Making Framework for Formulation Selection

A rational formulation development strategy should consider:

Drug Factors

- Solubility
- Log P
- Dose
- Stability
- Melting point

Formulation Factors

- Drug loading
- Release profile
- Scalability
- Cost

Regulatory Factors

- Excipient safety

- Manufacturing reproducibility
- Quality control requirements

Table 32: Comprehensive Comparison of Formulation Strategies for BCS Class-II Antidiabetic Drugs

Technology	Solubility Enhancement	Stability	Drug Loading	Scale-Up Potential	Clinical Potential
Micronization	Moderate	High	Excellent	Excellent	Moderate
Solid Dispersion	High	Moderate	Good	Excellent	High
SEDDS	Very High	High	High	Excellent	Very High
SNEDDS	Very High	High	High	Excellent	Very High
Nanoemulsion	Very High	Moderate	High	Good	Very High
SLNs	High	High	Moderate	Good	High
NLCs	Very High	High	High	Good	Very High
Polymeric Nanoparticles	High	High	High	Moderate	High
Polymeric Micelles	Very High	Moderate	Moderate	Moderate	High
Inclusion Complexes	Moderate	High	Moderate	Excellent	Moderate

REFERENCES

1. Noyes, A. A., & Whitney, W. R. (1897). The rate of solution of solid substances in their own solutions. Journal of the American Chemical Society, 19(12), 930–934.
2. Chiou, W. L., & Riegelman, S. (1971). Pharmaceutical applications of solid dispersion systems. Journal of Pharmaceutical Sciences, 60(9), 1281–1302.
3. Hancock, B. C., & Parks, M. (2000). What is the true solubility advantage for amorphous pharmaceuticals? Pharmaceutical Research, 17(4), 397–404.
4. Peppas, N. A., Bures, P., Leobandung, W., & Ichikawa, H. (2000). Hydrogels in pharmaceutical formulations. European Journal of Pharmaceutics and Biopharmaceutics, 50(1), 27–46.
5. Dressman, J., Butler, J., Hempenstall, J., & Reppas, C. (2001). The BCS: Where do we go from here? Pharmaceutical Technology, 25(7), 68–76.
6. Müller, R. H., Radtke, M., & Wissing, S. A. (2002). Nanostructured lipid matrices for improved microencapsulation of drugs. International Journal of Pharmaceutics, 242(1–2), 121–128.
7. Yu, L. X., Amidon, G. L., Polli, J. E., et al. (2002). Biopharmaceutics Classification System: The scientific basis for biowaiver extensions. Pharmaceutical Research, 19(7), 921–925.
8. Agnihotri, S. A., Mallikarjuna, N. N., & Aminabhavi, T. M. (2004). Recent advances on chitosan-based micro- and nanoparticles in drug delivery. Journal of Controlled Release, 100(1), 5–28.
9. Müller, R. H., & Keck, C. M. (2004). Challenges and solutions for the delivery of poorly soluble drugs. European Journal of Pharmaceutics and Biopharmaceutics, 58(2), 343–356.
10. Lennernäs, H., & Abrahamsson, B. (2005). The use of biopharmaceutic classification of drugs in drug discovery and development. Journal of Pharmacy and Pharmacology, 57(3), 273–285.
11. Tomalia, D. A., Reyna, L. A., & Svenson, S. (2005). Dendrimers as multi-purpose nanodevices for oncology drug delivery and diagnostic imaging. Biochemical Society Transactions, 33, 61–67.
12. Pouton, C. W. (2006). Formulation of self-emulsifying drug delivery systems. Advanced Drug Delivery Reviews, 60(6), 625–637.

13. Porter, C. J. H., Trevaskis, N. L., & Charman, W. N. (2007). Lipids and lipid-based formulations in drug delivery. Nature Reviews Drug Discovery, 6(3), 231–248.
14. Torchilin, V. P. (2007). Micellar nanocarriers: Pharmaceutical perspectives. Nature Reviews Drug Discovery, 6(2), 145–160.
15. Vallet-Regí, M., Balas, F., & Arcos, D. (2007). Mesoporous materials for drug delivery. Angewandte Chemie International Edition, 46(40), 7548–7558.
16. Benet, L. Z., Amidon, G. L., Barends, D., et al. (2008). The use of the Biopharmaceutics Classification System in drug development. The AAPS Journal, 10(1), 208–212.
17. Andrews, G. P., Laverty, T. P., & Jones, D. S. (2009). Mucoadhesive polymeric platforms for controlled drug delivery. European Journal of Pharmaceutics and Biopharmaceutics, 71(3), 505–518.
18. Brittain, H. G. (2009). Polymorphism in pharmaceutical solids (2nd ed.). Informa Healthcare.
19. Loftsson, T., & Brewster, M. E. (2010). Pharmaceutical applications of cyclodextrins: Basic science and product development. Journal of Pharmacy and Pharmacology, 62(11), 1607–1621.
20. Kawabata, Y., Wada, K., Nakatani, M., et al. (2011). Formulation design for poorly water-soluble drugs based on biopharmaceutics classification system. International Journal of Pharmaceutics, 420(1), 1–10.
21. Makadia, H. K., & Siegel, S. J. (2011). Poly(lactic-co-glycolic acid) as biodegradable controlled drug delivery carrier. Polymers, 3(3), 1377–1397.
22. McClements, D. J. (2012). Nanoemulsions versus microemulsions: Terminology, differences, and similarities. Soft Matter, 8(6), 1719–1729.
23. Savjani, K. T., Gajjar, A. K., & Savjani, J. K. (2012). Drug solubility: Importance and enhancement techniques. ISRN Pharmaceutics, 2012, 195727.
24. Danhier, F., Ansorena, E., Silva, J. M., et al. (2012). PLGA-based nanoparticles: An overview of biomedical applications. Journal of Controlled Release, 161(2), 505–522.
25. Williams, H. D., Trevaskis, N. L., Charman, S. A., et al. (2013). Strategies to address low drug solubility in discovery and development. Pharmacological Reviews, 65(1), 315–499.
26. Akbarzadeh, A., Rezaei-Sadabady, R., Davaran, S., et al. (2013). Liposome: Classification, preparation, and applications. Nanoscale Research Letters, 8(1), 102.
27. Kalepu, S., & Nekkanti, V. (2015). Insoluble drug delivery strategies: Review of recent advances and business prospects. Acta Pharmaceutica Sinica B, 5(5), 442–453.
28. Patel, A. R., Vavia, P. R., & Trotta, F. (2016). Cyclodextrin-based formulations for oral drug delivery. Current Drug Delivery, 13(3), 358–371.
29. Date, A. A., & Nagarsenker, M. S. (2017). Design and evaluation of self-nanoemulsifying drug delivery systems. Journal of Drug Delivery Science and Technology, 39, 233–245.
30. Kumar, R., & Sinha, V. R. (2018). Preparation and optimization of nanosuspensions for oral drug delivery. Drug Development and Industrial Pharmacy, 44(5), 747–758.
31. Shah, R., Eldridge, D., Palombo, E., & Harding, I. (2019). Lipid nanoparticles: Production, characterization and stability. Drug Delivery and Translational Research, 9(3), 723–736.
32. Patel, A., Shelat, P., Lalwani, A., & Liu, Q. (2020). Development and optimization of self-nanoemulsifying drug delivery systems.

Drug Development and Industrial Pharmacy, 46(4), 537–549.

33. Jaiswal, M., Dudhe, R., & Sharma, P. K. (2020). Nanoemulsion: An advanced mode of drug delivery system. Biotech, 5(2), 123–127.
34. Kumar, M., Bishnoi, R. S., & Shukla, A. K. (2021). Nanostructured lipid carriers: A promising drug delivery system. Current Pharmaceutical Design, 27(12), 1527–1542.
35. Singh, B., Bandopadhyay, S., & Kapil, R. (2021). Recent advances in lipid-based nanocarriers for oral drug delivery. Journal of Drug Delivery Science and Technology, 63, 102487.
36. Sharma, G., Kesarla, R., & Chotai, N. (2022). Polymeric nanoparticles for oral delivery of poorly soluble drugs. Pharmaceutics, 14(5), 1023.
37. Yadav, N., Khatak, S., & Saraogi, G. K. (2022). Solid lipid nanoparticles and nanostructured lipid carriers: Recent advances. Journal of Pharmaceutical Investigation, 52(2), 123–145.
38. Patel, H., Patel, V., & Shah, D. (2023). Recent trends in nanoemulsion technology for oral drug delivery. International Journal of Pharmaceutics, 635, 122691.
39. Gupta, A., Kumar, S., & Sharma, P. (2024). Advanced nanocarrier systems for enhancing oral bioavailability of poorly soluble drugs. Drug Delivery, 31(1), 233–248.
40. Zhang, Y., Liu, X., & Wang, J. (2025). Emerging strategies in lipid and polymeric nanocarriers for oral delivery of BCS Class-II drugs. Advanced Drug Delivery Reviews, 210, 115142.

HOW TO CITE: Chetan Jain, Dr. Vaibhavkumar Jagtap, Formulation Strategies to Enhance the Bioavailability of BCS Class-II Antidiabetic Drugs: Current Advances and Future Perspectives, Int. J. of Pharm. Sci., 2026, Vol 4, Issue 6, 5967-6001. https://doi.org/10.5281/zenodo.20815200