RESEARCH PAPER

Dissolution Cubes for Enhancement of Bioavailability of BCS Class II Drugs: A Comprehensive Pharmaceutical Review

Balachandra M[1] and Kumar CSP[*2]

[1]*Research Scholar, Bir Tikendrajit University, Canchipur, Imphal West-795003, Manipur, India*
[2]*Research Supervisor, Bir Tikendrajit University, Canchipur, Imphal West-795003, Manipur, India*
[*2]*chsphanikumar@gmail.com*

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ABSTRACT
Biopharmaceutics Classification System (BCS) Class II drugs exhibit high membrane permeability but poor aqueous solubility, making dissolution the rate-limiting step in oral absorption. Numerous formulation strategies have been developed to overcome dissolution-limited bioavailability. The concept of **"**dissolution cubes**"**—a surface area amplification approach based on geometric subdivision and structural modification of drug particles or carriers—represents an emerging conceptual framework aligning with particle engineering, porous systems, and nanostructured formulations. By increasing effective surface area and reducing diffusion path length, dissolution cubes enhance dissolution rate according to the Noyes–Whitney equation. This review critically discusses the pharmaceutical basis, suitability criteria, preparation methods, evaluation strategies, recent literature advances, marketed product parallels, regulatory perspectives, and future directions in applying dissolution cube-based approaches to BCS Class II drugs.
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1. INTRODUCTION

1.1. BCS Class II Drugs and Dissolution-Limited Absorption

The Biopharmaceutics Classification System (BCS) provides a scientific framework for categorizing drug substances based on two critical parameters influencing oral absorption: aqueous solubility and intestinal permeability. According to this system, drugs are divided into four classes. BCS Class II drugs are characterized by low aqueous solubility and high permeability, meaning that although they readily cross biological membranes, their limited dissolution in gastrointestinal fluids restricts the rate and extent of systemic absorption.

For BCS Class II drugs, dissolution in the gastrointestinal tract becomes the rate-limiting step in the absorption process. After oral administration, a drug must first dissolve in gastric or intestinal fluids before it can permeate through the intestinal epithelium into systemic circulation. Even when the permeability across the intestinal membrane is high, inadequate dissolution results in suboptimal drug concentration in solution, thereby reducing the driving force for absorption. Consequently, these drugs often exhibit poor and variable bioavailability, delayed onset of action, and significant inter-individual variability. This issue becomes particularly critical for drugs with narrow therapeutic windows or those requiring rapid therapeutic action. Food effects may further complicate absorption by altering gastrointestinal pH, motility, and bile salt secretion, which can either enhance or inhibit dissolution. Hence, formulation strategies for BCS Class II drugs primarily focus on improving dissolution behaviour rather than permeability enhancement. Representative examples of BCS Class II drugs include Itraconazole, a highly lipophilic antifungal agent with extremely low aqueous solubility; Atorvastatin, widely prescribed for hyperlipidaemia but limited by dissolution-dependent absorption; Cefuroxime axetil, an ester prodrug with poor water solubility; and Griseofulvin, historically known for improved bioavailability through micronization. These examples illustrate the pharmaceutical challenge posed by dissolution-limited drugs and underscore the need for innovative strategies to enhance their oral performance[1,2].

1.2. Theoretical Basis of Dissolution Enhancement

The rate of dissolution of a solid drug particle in a liquid medium is quantitatively described by the Noyes–Whitney equation:

**Author for Correspondence: chsphanikumar@gmail.com*

$$\frac{dC}{dt} = \frac{DA(Cs-C)}{h}$$

Where:

D = diffusion coefficient of the drug

A = surface area of the dissolving solid

C_s = saturation solubility of the drug

C = concentration of drug in the bulk solution at time t

h = thickness of the diffusion boundary layer

This equation highlights the parameters that govern dissolution kinetics. Enhancement strategies can therefore target:

1. Increasing the saturation solubility (Cs)

2. Reducing diffusion layer thickness (h)

3. Increasing diffusion coefficient (D)

4. Increasing surface area (A)

Among these variables, surface area (A) is the most practical and controllable parameter in pharmaceutical formulation. According to particle size reduction principles, decreasing particle size dramatically increases surface area, which proportionally enhances dissolution rate. For instance, reducing particle size from micrometer to nanometer scale increases the surface-to-volume ratio exponentially, leading to faster dissolution. Moreover, amorphization, porosity enhancement, and dispersion in hydrophilic carriers can indirectly increase the effective surface area exposed to dissolution media. Therefore, pharmaceutical technologies such as micronization, nanonization, solid dispersion, and porous carrier systems are fundamentally rooted in the manipulation of surface area and diffusion dynamics[3].

1.3. Concept of "Dissolution Cubes"

The concept of "dissolution cubes" is derived from a simple geometric principle:

- A single large cube possesses a fixed and limited surface area.
- If that cube is subdivided into multiple smaller cubes of equal total volume, the cumulative surface area increases significantly.

For example, if a cube is divided into eight smaller cubes, the total surface area doubles, even though the overall volume remains constant. This geometric amplification of surface area provides a conceptual model for understanding dissolution enhancement strategies in pharmaceutical sciences.

Translating this geometric analogy into pharmaceutical practice involves structural and morphological engineering of drug particles or carriers. The dissolution cube approach encompasses:

- Particle subdivision through micronization or nanocrystal formation
- Porous cube-like carriers that increase internal surface area
- Nano- or micro-structured cubic particles

Fragmented matrices designed to disintegrate into high-surface-area units

This concept aligns closely with established and emerging technologies such as nanocrystal engineering, where drug particles are reduced to nanoscale dimensions to maximize surface exposure; porous silica drug loading, which traps drug molecules within high-surface-area matrices; micro-structured solid dispersions, which distribute drug in hydrophilic polymer networks; and advanced 3D-printed cubic dosage forms that enable controlled geometry and internal porosity. In essence, the dissolution cube concept provides a unifying theoretical framework that integrates particle engineering, surface modification, and structural design principles to enhance dissolution rates. By increasing the effective surface area available for interaction with gastrointestinal fluids, such systems significantly improve dissolution kinetics and, consequently, oral bioavailability of BCS Class II drugs. As pharmaceutical research advances toward precision formulation and geometry-controlled drug delivery systems, the dissolution cube model offers both a conceptual and practical foundation for designing next-generation oral dosage forms that overcome solubility limitations and optimize therapeutic performance[4,5]

Table 1: Recent Works on Surface Area–Driven Dissolution Enhancement

Year	Strategy	Drug	Key Outcome
2025	Deep eutectic system	Cefuroxime axetil	3–5 fold solubility increase
2024	Nano-solid dispersion	Itraconazole	Improved tablet dissolution stability
2023	Liquisolid technique	Mosapride citrate	~70% dissolution vs ~15% conventional
2023	Nanocrystal engineering	Atorvastatin	Faster onset and higher Cmax
2022	Porous silica loading	Fenofibrate	Amorphous stabilization

Table 2: Marketed Products Reflecting Dissolution Cube Principles

Product	Drug	Strategy	Mechanism
Sporanox®	Itraconazole	Solid dispersion	Amorphous form ↑ dissolution
Lipitor®	Atorvastatin	Nanocrystal	Surface area enhancement

Gris-PEG®	Griseofulvin	Micronization	Reduced particle size
Tricor®	Fenofibrate	Micronized formulation	Improved dissolution

2. SUITABILITY OF DRUGS FOR DISSOLUTION CUBE STRATEGY

2.1. Drug Selection Criteria

Table 3: Suitable BCS Class II Drugs

Drug	Therapeutic Class	Suitability Rationale
Itraconazole	Antifungal	Extremely poor solubility; benefits from amorphous and nano forms
Atorvastatin	Antihyperlipidemic	Bioavailability enhanced via nanocrystals
Cefuroxime axetil	Antibiotic	Dissolution-limited absorption
Fenofibrate	Hypolipidemic	Lipophilic; porous systems improve release
Carbamazepine	Antiepileptic	Polymorphic; dissolution dependent

3. BACK GROUND OF THE WORK

Recent advancements in dissolution enhancement of BCS Class II drugs increasingly emphasize particle engineering, solid-state modification, and structural design approaches that align with the "dissolution cube" concept. These strategies focus on increasing effective surface area, reducing crystallinity, and optimizing drug–carrier interactions to overcome dissolution-limited bioavailability[6-10].

3.1. Nanocrystal Engineering

Nanocrystal technology has emerged as one of the most successful and industrially scalable approaches for enhancing dissolution. This strategy involves reducing drug particle size to the nanometer range (typically 100–1000 nm), thereby significantly increasing surface area and dissolution rate according to the Noyes–Whitney equation. Common preparation methods include wet milling (media milling) and high-pressure homogenization. In wet milling, coarse drug particles are subjected to mechanical attrition in the presence of stabilizers and milling media, leading to progressive size reduction. High-pressure homogenization forces drug suspensions through narrow gaps under intense pressure, generating shear forces and cavitation that reduce particle size to the nanoscale. A critical aspect of nanocrystal systems is stabilization. Due to the high surface energy of nanoparticles, aggregation is a major challenge. Therefore, polymers and surfactants such as hydroxypropyl methylcellulose (HPMC), polyvinylpyrrolidone (PVP), poloxamers, and sodium dodecyl sulphate are used to provide steric or electrostatic stabilization. Nanocrystals typically achieve a 10–100-fold increase in surface area, resulting in dramatically enhanced dissolution velocity. Additionally, nanosizing may slightly increase apparent saturation solubility due to increased curvature effects (Kelvin equation). Several marketed formulations of poorly soluble drugs utilize nanocrystal technology, demonstrating its clinical and regulatory acceptance.

3.2. Amorphous Solid Dispersions (ASDs)

Amorphous solid dispersions represent another major advancement in dissolution enhancement. Unlike crystalline drugs, amorphous forms lack long-range molecular order and therefore do not require crystal lattice energy to dissolve. This results in higher apparent solubility and faster dissolution. Preparation methods include hot-melt extrusion (HME) and spray drying, both widely adopted in pharmaceutical manufacturing. In hot-melt extrusion, the drug is blended with a polymer carrier and processed under heat and mechanical shear to form a homogeneous amorphous matrix. Spray drying involves dissolving the drug and polymer in a suitable solvent, followed by rapid solvent evaporation to form amorphous particles. Common polymer carriers include HPMC, PVP, copovidone, and Soluplus®. These polymers not only stabilize the amorphous form but also inhibit recrystallization by molecular interactions such as hydrogen bonding.

The primary mechanism involves elimination of crystal lattice energy, allowing the drug to dissolve more readily. Furthermore, ASDs generate a supersaturated solution upon dissolution, often referred to as the "spring and parachute" effect—rapid generation of high drug concentration (spring) followed by stabilization of supersaturation (parachute). This leads to enhanced absorption before precipitation occurs.

However, long-term physical stability remains a critical consideration, as amorphous forms may recrystallize under stress conditions.

3.3. Porous Drug Carriers

Porous carrier systems enhance dissolution by dramatically increasing internal surface area and improving wettability. These systems align strongly with the dissolution cube analogy, as they introduce internal channels and void spaces that multiply the available surface for dissolution. Common materials include mesoporous silica, porous microcubes, and sugar-based porous matrices. Mesoporous silica materials, such as MCM-41 or SBA-15, possess well-defined pore structures (2–50 nm) that can entrap drug molecules in an amorphous or molecularly dispersed state. The confinement of drug molecules within nanopores prevents crystallization and increases dissolution rate. Porous microcubes fabricated through templating or freeze-drying techniques provide structural advantages by

offering controlled pore size distribution and high drug loading capacity. Similarly, sugar-based porous carriers (e.g., porous lactose or mannitol) improve dissolution through capillary action and rapid disintegration.

Key advantages include:

- High drug loading efficiency
- Improved wettability and rapid media penetration
- Controlled diffusion pathways

These systems can also be integrated with sustained-release or targeted delivery mechanisms.

3.4. Deep Eutectic Systems

Deep eutectic systems (DES) represent a relatively recent approach to enhancing solubility and dissolution. These systems are formed by combining two or more components (e.g., hydrogen bond donors and acceptors) that interact to form a eutectic mixture with a melting point significantly lower than that of individual components. In pharmaceutical applications, DES can disrupt crystal packing of poorly soluble drugs, leading to improved molecular mobility and enhanced thermodynamic solubility. The mechanism involves disruption of crystal lattice structure, reduction of cohesive energy, and stabilization of drug molecules in a more soluble state. DES-based formulations may generate and maintain supersaturated drug concentrations, thereby enhancing absorption. Additionally, they offer advantages such as ease of preparation, potential biocompatibility, and tuneable physicochemical properties. However, toxicity and regulatory considerations require careful evaluation.

3.5. 3D Printing and Structured Cubes

An emerging frontier in dissolution enhancement involves 3D printing technologies for fabricating structured cubic dosage forms. This approach enables precise control over geometry, porosity, and internal architecture, aligning closely with the dissolution cube concept. Using techniques such as fused deposition Modelling (FDM) or selective laser sintering (SLS), researchers can fabricate cubic porous matrices with predetermined surface area and internal channels. By modifying infill density and pore size, dissolution profiles can be customized.

Advantages include:

- Geometry-driven dissolution control
- Personalized dosing and tailored release profiles
- On-demand manufacturing

Structured cubes can incorporate multiple drugs or layers with distinct release characteristics, opening new possibilities for individualized therapy.

Table 4: Literature review

S.No.	Drug (Example)	Method	Purpose
1	Itraconazole	Wet milling (media milling)	Reduce particle size to nanometer range to increase surface area and enhance dissolution rate
2	Fenofibrate	High-pressure homogenization	Produce stable nanocrystals to improve dissolution velocity and oral bioavailability
3	Atorvastatin	Nanocrystal stabilization using HPMC/PVP/poloxamers	Prevent aggregation of nanoparticles and maintain enhanced surface area for faster dissolution
4	Carbamazepine	Hot-melt extrusion (Amorphous Solid Dispersion)	Eliminate crystal lattice energy and enhance apparent solubility
5	Itraconazole	Spray drying with polymer carriers (HPMC, PVP, Soluplus®)	Generate amorphous solid dispersion to produce supersaturation and improve absorption
6	Cefuroxime axetil	Mesoporous silica loading (MCM-41, SBA-15)	Increase internal surface area and prevent recrystallization for improved dissolution
7	Griseofulvin	Porous sugar-based carriers (porous lactose/mannitol)	Enhance wettability and promote rapid disintegration and dissolution
8	Cefuroxime axetil	Deep eutectic system formulation	Disrupt crystal packing and improve thermodynamic solubility with stabilized supersaturation
9	Ibuprofen	Deep eutectic mixture formation	Reduce cohesive energy and enhance dissolution behaviour
10	Levetiracetam	3D printing (FDM/SLS) of cubic porous matrices	Enable geometry-driven dissolution control and personalized dosing
11	Paracetamol	3D printed structured cubes with controlled infill density	Customize surface area and tailor drug release profiles

4. METHODS OF PREPARATION OF DISSOLUTION CUBES

Dissolution cubes represent an advanced structural drug delivery concept in which the geometry, internal architecture, porosity, and surface characteristics of a cubic dosage unit are deliberately engineered to maximize surface exposure and control drug release. Unlike conventional dissolution enhancement strategies that focus primarily on particle size reduction or molecular dispersion, dissolution cubes integrate geometric design, material science, and controlled porosity engineering to optimize dissolution behaviour. The cube geometry provides uniform surface distribution, predictable erosion patterns, and customizable internal channels that facilitate rapid penetration of gastrointestinal fluids. Preparation of dissolution cubes therefore involves structural fabrication techniques rather than simple size-reduction processes. The methods described below focus specifically on engineering cubic matrices with tailored dissolution characteristics[11-18].

4.1. Direct Compression-Based Cube Formation

One of the simplest approaches to prepare dissolution cubes involves compressing drug–excipient blends into cubic moulds instead of conventional round tablet punches. In this method, the drug is blended with hydrophilic polymers (e.g., HPMC, PVP), super-disintegrants, and pore-forming agents. The mixture is then compressed using specially designed cubic dies. The uniqueness of this method lies in geometric optimization. The cube shape provides increased edge and corner surface exposure compared to cylindrical tablets. Corners act as stress concentration points where erosion and dissolution initiate more rapidly. By adjusting compression force, porogen concentration, and polymer viscosity, the internal compactness and dissolution rate can be controlled.

Advantages of this method include simplicity, scalability, and compatibility with existing tableting equipment (with minor tooling modification). However, mechanical strength must be carefully optimized to prevent edge chipping during handling.

4.2. Porogen-Leaching Technique

Porogen leaching is a structural engineering method used to create highly porous cubic matrices. In this approach, water-soluble pore-forming agents such as sodium chloride, mannitol, or sugars are incorporated into the drug–polymer blend before cube compression or moulding. After forming the cube, the system is exposed to a solvent (often water) that selectively dissolves the porogen, leaving behind interconnected pores. These pores significantly increase internal surface area and facilitate rapid fluid penetration.

The porosity level can be precisely controlled by adjusting the type, size, and concentration of the porogen. Higher porogen content leads to greater porosity and faster dissolution, while lower levels provide sustained release. This technique is particularly useful for poorly soluble drugs requiring enhanced wettability and diffusion pathways.

The main limitation is the additional processing step required for porogen removal and drying, which may increase manufacturing time.

4.3. Freeze Casting (Directional Freezing)

Freeze casting is an advanced technique used to fabricate highly porous dissolution cubes with aligned internal channels. In this method, a drug–polymer solution or suspension is poured into cubic molds and subjected to controlled freezing. As ice crystals form, they push dissolved and suspended materials into concentrated regions. Subsequent sublimation under vacuum (lyophilization) removes the ice crystals, leaving behind a porous scaffold that mirrors the ice crystal pattern. The result is a cube with interconnected microchannels that dramatically enhance liquid penetration and surface exposure. Directional freezing allows control over pore orientation. For example, vertically aligned channels can promote rapid axial fluid transport. Freeze-cast cubes exhibit extremely fast disintegration and dissolution due to their lightweight, sponge-like structure.

Although highly effective, freeze casting requires specialized equipment and careful temperature control, making it more suitable for high-value formulations.

4.4. 3D Printing of Dissolution Cubes

Additive manufacturing (3D printing) has revolutionized the fabrication of complex dosage forms. Dissolution cubes can be prepared using techniques such as fused deposition Modelling (FDM), semi-solid extrusion, or binder jet printing. In FDM-based printing, drug-loaded polymer filaments are extruded layer by layer to build a cube with precisely defined infill density and internal architecture. By adjusting infill percentage, layer thickness, and pattern design, the dissolution profile can be customized. Low infill creates highly porous cubes with rapid release, while dense infill results in slower dissolution.

Binder jet printing involves selectively depositing a liquid binder onto a powder bed in cubic patterns. The printed cube is then dried and strengthened. This approach allows incorporation of high drug loads and rapid disintegration properties.

The greatest advantage of 3D printing lies in personalization. Cube size, porosity, and drug dose can be digitally modified to suit individual patient needs. However, regulatory standardization and large-scale production remain challenges.

4.5. Gas Foaming Technique

Gas foaming introduces gas-generating agents into a polymeric cubic matrix. Upon activation—either by heat or chemical reaction—gas bubbles form within the structure, creating a porous internal network. For example, incorporation of sodium bicarbonate with an acid source can generate carbon dioxide when exposed to moisture.

The evolving gas forms interconnected pores throughout the cube. Increased pore volume enhances fluid ingress and accelerates dissolution.

This method is relatively simple and cost-effective. However, controlling pore size uniformity can be challenging, and mechanical strength must be balanced with porosity.

4.6. Solvent Casting and Mold Solidification

In solvent casting, the drug and polymer are dissolved or dispersed in a suitable solvent system. The mixture is poured into cubic moulds and allowed to solidify through solvent evaporation.

As the solvent evaporates, the drug becomes embedded within a polymeric matrix. By manipulating solvent evaporation rate and polymer concentration, internal microstructure can be controlled. Slow evaporation promotes dense matrices, while rapid evaporation may induce microvoid formation.

This method is particularly useful for incorporating hydrophilic carriers and producing amorphous dispersions within cubic geometries. However, complete solvent removal must be ensured to meet safety standards.

4.7. Hybrid Lipid–Polymer Cubic Fabrication

Hybrid cubic matrices combine lipid-based solubilisation systems with rigid polymeric cubic scaffolds. The drug is first dissolved in a lipid phase to enhance solubility, and the lipid system is then embedded within a porous polymer cube. Such systems improve wettability and may promote lymphatic absorption for lipophilic drugs. The cubic scaffold provides mechanical strength and geometric stability, while the lipid component enhances dissolution and solubilization.

Preparation typically involves emulsification followed by moulding or extrusion into cubic forms. This dual mechanism approach is promising for drugs with extremely poor aqueous solubility.

4.8. Continuous Extrusion-Based Cube Manufacturing

Continuous manufacturing processes can be adapted to produce cubic dosage forms by combining hot-melt extrusion with inline moulding systems. Drug–polymer melts are extruded and cut into uniform cubic segments. Process Analytical Technology (PAT) tools monitor temperature, viscosity, and drug distribution in real time. Continuous production enhances uniformity, scalability, and cost-efficiency.

Overall, preparation of dissolution cubes has evolved into a sophisticated structural engineering discipline. Unlike conventional dissolution enhancement strategies focused solely on particle size reduction, dissolution cubes emphasize geometry-driven surface optimization, internal porosity design, and controlled architectural engineering. Techniques such as porogen leaching, freeze casting, gas foaming, solvent casting, hybrid lipid incorporation, 3D printing, and continuous extrusion allow precise control over dissolution behavior. The optimal preparation method depends on drug solubility, desired release kinetics, mechanical strength requirements, scalability considerations, and regulatory acceptance.

Through rational design and advanced fabrication technologies, dissolution cubes offer a promising platform for next-generation oral drug delivery systems.

Love this topic — dissolution cubes are basically pharmaceutical architecture meets drug delivery science. Let’s build a comprehensive, cube-specific evaluation table that focuses on geometry, porosity engineering, internal architecture, and structural performance (not just conventional dissolution enhancement metrics).

Table 5: Evaluation Framework for Dissolution Cubes

Category	Primary Objective	Specific Parameters	Analytical Techniques / Tools	Scientific Relevance in Dissolution Cubes
Geometric & Dimensional Analysis	Confirm cube geometry precision and uniformity	Edge length, surface area, volume, edge sharpness, dimensional deviation	Digital calipers, Optical microscopy, 3D laser scanning, Micro-CT	Geometry directly influences surface exposure, edge erosion behavior, and dissolution predictability
Internal Architecture Characterization	Evaluate engineered internal channels and pore networks	Channel alignment, infill density (3D printed cubes), scaffold integrity	Micro-CT imaging, SEM cross-section analysis	Determines fluid penetration pathways and directional dissolution behavior
Porosity & Pore Structure Analysis	Quantify total porosity and pore distribution	Total porosity (%), pore size distribution, pore interconnectivity	BET surface area analysis, Mercury intrusion porosimetry, Gas adsorption studies	Higher porosity increases surface area and accelerates fluid ingress
Surface Morphology Evaluation	Assess external cube surface characteristics	Surface roughness, microcracks, edge integrity	SEM, Atomic Force Microscopy (AFM)	Rough surfaces enhance wettability and initial dissolution rate
Mechanical Strength Testing	Ensure structural stability during handling	Crushing strength, edge friability, tensile strength	Texture analyzer, Hardness tester, Friability testing	Critical to prevent edge chipping and maintain geometric advantages
Wettability & Fluid Penetration Studies	Evaluate interaction with GI fluids	Contact angle, capillary rise, swelling index	Contact angle goniometer, Gravimetric swelling analysis	Determines speed of liquid ingress and initiation of erosion
Solid-State Characterization	Confirm drug structural integrity post-fabrication	Crystallinity, amorphization, polymorphic transitions	DSC, PXRD, FTIR	Ensures fabrication processes (e.g., freeze casting, extrusion) do not compromise stability
Density & Internal Compactness	Measure matrix compactness and structural uniformity	True density, bulk density, apparent density	Helium pycnometry, Density measurement	Influences dissolution kinetics and erosion pattern
Dissolution Performance Testing	Assess in vitro drug release behavior	% drug release vs time, dissolution rate constant	USP Apparatus I & II, Flow-through cell apparatus	Establishes geometry-driven release enhancement
Biorelevant Dissolution Testing	Simulate physiological GI environment	Release in fasted/fed conditions	FaSSIF, FeSSIFmedia studies	Predicts real GI fluid interaction with porous cube matrix
Erosion & Disintegration Pattern Study	Visualize structural breakdown behavior	Edge erosion rate, corner disintegration time	Time-lapse imaging, Gravimetric erosion study	Confirms cube-specific erosion initiation at edges and corners
Release Kinetics Modelling	Define mechanism of drug release	Zero-order, First-order, Higuchi, Korsmeyer–Peppas	Mathematical Modelling software	Identifies diffusion vs erosion vs architecture-driven release
*In Vivo*Pharmacokinetics	Validate enhanced absorption	Cmax, Tmax, AUC	Animal/human PK studies	Confirms geometry-porosity translation into bioavailability improvement
Stability Studies	Ensure long-term performance retention	Structural stability, recrystallization, moisture sensitivity	ICH stability testing, PXRD monitoring, SEM over time	Prevents pore collapse, edge deformation, or recrystallization
Process Monitoring (Continuous Manufacturing)	Ensure reproducibility in advanced fabrication	Melt viscosity, extrusion temperature, drug uniformity	Process Analytical Technology (PAT), NIR spectroscopy	Essential for extrusion-based or 3D-printed cube production

Dissolution cube evaluation uniquely emphasizes:

- Geometric precision validation
- Internal architectural imaging
- Porosity engineering quantification
- Edge-driven erosion studies
- Structure–function correlation

Unlike traditional systems focused primarily on particle size reduction or amorphization, dissolution cube assessment integrates structural engineering principles with pharmaceutical evaluation.

6. CURRENT TRENDS IN DISSOLUTION CUBE TECHNOLOGY

Dissolution cubes represent a paradigm shift from conventional dissolution enhancement toward geometry-driven, structurally engineered drug delivery systems. Current research trends focus on architectural precision, digital fabrication, predictive Modelling, continuous structural manufacturing, and regulatory alignment. Unlike traditional systems centered on particle modification alone, dissolution cubes integrate material science, computational Modelling, and structural optimization to achieve programmable drug release.

The following emerging trends highlight how dissolution cube platforms are evolving into next-generation oral delivery systems[19-25].

6.1. Geometry-Driven Quality by Design (Structural QbD)

Quality by Design (QbD) principles are increasingly being adapted specifically for structural dosage forms such as dissolution cubes.

In structural QbD:

Quality Target Product Profile (QTPP) includes geometric precision, pore architecture, mechanical strength, and release kinetics.

Critical Quality Attributes (CQAs) include:

- Cube edge length uniformity
- Surface area-to-volume ratio
- Porosity percentage
- Internal channel alignment
- Dissolution rate profile

Critical Process Parameters (CPPs) include compression force, freezing rate (freeze casting), extrusion temperature, and 3D printing infill density.

Design of Experiments (DoE) is used to optimize porogen concentration, polymer viscosity, and geometric parameters simultaneously.

This structural QbD approach ensures reproducible cube fabrication and strengthens regulatory acceptance.

6.2. AI-Assisted Structural Optimization

Artificial Intelligence (AI) and machine learning are increasingly used to predict how cube geometry influences dissolution behaviour.

Applications include:
- Predicting optimal infill density in 3D-printed cubes
- Modelling pore network formation in porogen-leached systems
- Simulating fluid penetration patterns using computational fluid dynamics (CFD)

6.3. Advanced 3D Printing & Personalized Cube Design

Additive manufacturing is one of the most transformative trends for dissolution cubes.

Modern 3D printing platforms allow:
- Patient-specific cube dimensions
- Adjustable drug dose by modifying cube volume
- Customizable infill architecture for immediate or sustained release
- Multi-drug compartmentalized cubes

Digitally tuneable cube architecture enables on-demand manufacturing in hospital or pharmacy settings. This aligns strongly with the global shift toward personalized medicine. However, regulatory standardization of printed cubic dosage forms remains an ongoing challenge.

6.4. Hierarchical Porosity Engineering

Emerging research focuses on multi-scale porosity within dissolution cubes:
- Macropores: Rapid fluid entry
- Mesopores: Increased internal surface area
- Micropores: Controlled diffusion pathways

Techniques such as combined porogen-leaching and freeze casting create hierarchical pore networks. This allows precise control of dissolution kinetics without altering chemical composition. Hierarchical design enhances wettability, reduces diffusion resistance, and enables programmable erosion patterns.

6.5. Hybrid Lipid–Polymer Structural Cubes

Hybrid systems integrating lipid solubilization within porous polymer cubes are gaining attention.

In these systems:
- The lipid phase improves solubility of lipophilic drugs
- The polymer cube provides mechanical stability and geometric control
- Nanochannels enhance diffusion and wettability

Such structural hybrids may promote lymphatic absorption and reduce first-pass metabolism for highly lipophilic drugs. This dual-mechanism strategy combines solubilization with geometry-driven dissolution enhancement.
- Forecasting edge erosion rates based on material properties

Digital twin models can simulate cube erosion and drug diffusion in silico before physical production, significantly reducing experimental workload. This data-driven approach accelerates development and enables geometry-based personalization.

6.6. Continuous Structural Manufacturing

Continuous manufacturing technologies are being adapted for cubic dosage forms through:
- Hot-melt extrusion followed by inline cubic cutting
- Automated moulding systems
- Real-time porosity monitoring via Process Analytical Technology (PAT)

Advantages include:
- High uniformity
- Improved scalability
- Reduced batch-to-batch variability
- Real-time quality control

Regulatory agencies increasingly favor continuous manufacturing due to its consistency and traceability.

6.7. Advanced Imaging & *IVIVC* Modelling for Cubic Systems

Regulatory emphasis is shifting toward demonstrating strong *in vitro–in vivo correlation* (*IVIVC*) specifically for structurally engineered dosage forms.

For dissolution cubes, *IVIVC* Modelling now integrates:
- Micro-CT-based structural imaging
- CFD-based fluid penetration Modelling
- Erosion mapping
- Pharmacokinetic simulation

Establishing Level A *IVIVC* for geometry-driven systems enables:
- Reduced bioequivalence studies
- Faster regulatory approval
- Greater post-approval flexibility

As dissolution cubes become more architecturally complex, predictive *IVIVC* Modelling becomes essential for regulatory success.

Table 6: Current Trends in Dissolution Cube Technology

Trend	Core Principle	Key Technologies	Advantages	Challenges	Regulatory Impact
Structural QbD	Geometry- and porosity-driven quality control	DoE, Risk assessment, PAT	Reproducible architecture, reduced variability	Requires detailed structural mapping	Strongly encouraged
AI-Assisted Structural Optimization	Predictive Modelling o f cube dissolution	Machine learning, CFD, Digital twins	Faster development, fewer trials	Data validation complexity	Emerging acceptance
Advanced 3D Printing	Digitally programmable cube fabrication	FDM, Binder jet printing, Semi-solid extrusion	Personalization , customizable release	Standardizatio n challenges	Under evolving frameworks
Hierarchical Porosity Engineering	Multi-scale pore architecture	Freeze casting + porogenleachin g	Controlled fluid ingress, programmable release	Complex fabrication control	Requires detailed characterizatio n
Hybrid Lipid–Polymer Cubes	Dual solubilization+ structural control	Emulsification, lipid embedding	Improved solubility + mechanical stability	Stability optimization	Requires comprehensive validation
Continuous Cube Manufacturing	Integrated structural production	Hot-melt extrusion, Inline molding, PAT	Scalability, uniformity, efficiency	High initial setup cost	Strong regulatory support
Advanced *IVIVC* Modellin g	Structure–function correlation	Micro-CT, PK Modelling, CFD	Reduced bioequivalence studies	Complex data integration	Critical for approval flexibility

Overall, current trends in dissolution cube technology reflect a shift toward:

- Geometry-driven pharmaceutical engineering
- Digital fabrication and personalization
- Hierarchical porosity control
- Predictive computational Modelling
- Continuous, regulatory-aligned production

Dissolution cubes are evolving from a conceptual structural innovation into a precision-engineered oral drug delivery platform capable of customizable, reproducible, and scalable performance.

7. APPLICATIONS OF DISSOLUTION CUBES

Dissolution cubes extend beyond a theoretical geometric innovation and demonstrate wide applicability across therapeutic areas where dissolution rate limits oral bioavailability. By engineering cubic dosage forms with optimized surface exposure, controlled porosity, and programmable internal architecture, dissolution cubes enhance drug–fluid interaction, improve wettability, and promote predictable erosion patterns. These properties make them particularly valuable for poorly water-soluble drugs, narrow therapeutic index compounds, and medications requiring rapid or controlled release.

Unlike conventional tablets, dissolution cubes offer architecture-driven release control, enabling both immediate and sustained delivery within a structurally stable framework. Their applications span antifungal therapy, cardiovascular management, neurological disorders, pain management, and antimicrobial treatment, while also providing key clinical advantages such as dose optimization, faster onset, and reduced pharmacokinetic variability[26-34].

7.1. Therapeutic Areas

Antifungals

Many antifungal agents are highly lipophilic and exhibit dissolution-limited absorption. Dissolution cubes enhance surface area and internal fluid penetration, improving systemic exposure. Porous cubic matrices or lipid–polymer hybrid cubes increase solubilization efficiency, supporting consistent plasma concentrations critical for systemic fungal infections.

Cardiovascular Drugs

Chronic cardiovascular therapies require stable plasma levels. Dissolution cubes with controlled porosity or engineered infill density provide predictable release kinetics and reduced interpatient variability, improving long-term blood pressure and lipid management.

Antiepileptics

Drugs with narrow therapeutic windows demand consistent absorption. Structurally uniform cubes reduce dissolution variability and ensure reproducible pharmacokinetics, minimizing fluctuations that may trigger breakthrough seizures.

NSAIDs

For pain and inflammatory conditions, rapid onset is desirable. High-edge-exposure cubic designs accelerate initial erosion and drug release, leading to faster therapeutic response. Enhanced bioavailability may also permit dose reduction, potentially minimizing gastrointestinal irritation.

Antibiotics
Prompt achievement of therapeutic concentrations is essential to prevent resistance. Highly porous dissolution cubes enable rapid fluid ingress and drug release, improving early plasma exposure and supporting effective infection control.

7.2. Clinical Advantages

- Dose Optimization: Improved dissolution efficiency increases systemic availability, potentially allowing lower doses while maintaining efficacy.
- Faster Onset of Action: Edge- and corner-driven erosion enhances early drug release.
- Reduced Interpatient Variability: Geometry-controlled dissolution minimizes the impact of physiological variability.
- Programmable Release Profiles: Adjusting cube porosity and architecture allows tailored immediate or sustained delivery.
- Improved Stability: Structured matrices protect amorphous or solubilized drug forms within a mechanically robust scaffold.

Table 7: Applications and Clinical Advantages of Dissolution Cubes

Therapeutic Area / Advantage	Common Challenge	Dissolution Cube Strategy	Clinical Benefit
Antifungals	Poor solubility, erratic absorption	Porous or lipid–polymer cubic matrices	Improved systemic exposure
Cardiovascular Drugs	Variable absorption	Controlled porosity cubes	Stable plasma concentrations
Antiepileptics	Narrow therapeutic index	Uniform structural design	Predictable pharmacokinetics
NSAIDs	Delayed onset, GI irritation	High surface-exposure cubes	Faster pain relief, possible dose reduction
Antibiotics	Sub-therapeutic exposure	Rapidly eroding porous cubes	Quick therapeutic levels
Dose Optimization	High dose toxicity	Enhanced dissolution efficiency	Reduced adverse effects
Faster Onset	Slow absorption	Edge-driven erosion	Earlier therapeutic response
Reduced Variability	Physiological differences	Geometry-controlled release	Consistent outcomes
Programmable Release	Fixed release profiles	Tuneable architecture	Personalized therapy potential

Overall, dissolution cubes represent a structurally engineered platform capable of addressing dissolution-limited drug absorption across multiple therapeutic categories. By combining geometric optimization with material science, they offer a versatile and scalable approach to next-generation oral drug delivery.

8. FUTURE PERSPECTIVES OF DISSOLUTION CUBES

The dissolution cube concept represents a convergence of geometric engineering, material science, and oral drug delivery design. Looking forward, the approach is poised to evolve into more sophisticated and responsive systems, addressing both patient-specific needs and complex pharmacokinetic challenges. Future developments are likely to focus on advanced cube architectures, functional responsiveness, and digital design integration[36-40].

8.1. Advanced Cube Designs

- Smart Porous Cubes: Future cubes may incorporate stimuli-sensitive materials that adjust pore size or surface properties in response to pH, temperature, or gastrointestinal enzymes. Such systems could optimize drug release dynamically along the GI tract.
- Stimuli-Responsive Dissolution Systems: Integration of polymers or excipients that respond to environmental triggers (e.g., ionic strength or redox conditions) could allow site-specific release or controlled supersaturation, enhancing bioavailability and reducing side effects.
- Hybrid Lipid–Polymer Cubic Matrices: Advanced cubes combining lipid phases with polymeric scaffolds can improve solubility for highly lipophilic drugs and support lymphatic absorption. Further optimization of internal geometry could enable programmable, multi-phase release profiles.

8.2. Digital and Manufacturing Integration

- AI-Designed Geometry-Based Dosage Forms: Artificial intelligence and computational Modelling may guide the design of cube

geometries, optimizing infill patterns, internal channels, and porosity to achieve target dissolution kinetics without extensive trial-and-error experimentation.

- 3D Printing and Additive Manufacturing: Personalized dissolution cubes could be printed with patient-specific doses, adjustable porosity, and controlled release profiles. This enables individualized therapy for populations such as paediatrics or geriatrics.
- Continuous Manufacturing Integration: Coupling hot-melt extrusion or in-line cube moulding with real-time monitoring ensures reproducible cubes at industrial scale, improving consistency and lowering production costs.

8.3. Personalized Medicine Applications

Dissolution cubes offer a platform for precision dosing, where geometry, porosity, and matrix composition can be tailored to individual pharmacokinetics, dietary patterns, and therapeutic targets. Integration with digital health platforms could further optimize dosing schedules and improve patient adherence.

Overall, dissolution cubes are likely to transition from a structural dissolution enhancement tool to a versatile, patient-centric delivery platform. Innovations in stimuli-responsiveness, AI-guided design, 3D printing, and hybrid matrices will define the next generation of oral drug delivery systems, combining efficiency, personalization, and regulatory readiness.

9. CONCLUSION

The dissolution cube approach represents an innovative, geometry-driven surface area amplification strategy firmly grounded in the principles of dissolution kinetics. By intentionally engineering drug particles or matrices into cubic architectures with optimized edge exposure, internal porosity, and controlled surface characteristics, this platform enhances drug–media interaction far beyond what conventional shape modification can achieve. For Biopharmaceutics Classification System (BCS) Class II drugs—where solubility and dissolution rate are the primary limitations to oral absorption—such structural modification directly addresses the rate-limiting step in bioavailability. Unlike traditional dissolution enhancement techniques that rely solely on particle size reduction or chemical modification, dissolution cubes integrate structural engineering with material science. The incorporation of hierarchical porosity, internal microchannels, and programmable architecture significantly improves wettability, accelerates fluid penetration, and promotes predictable erosion patterns. Modern advancements in nanotechnology, amorphous solid dispersions, lipid–polymer hybrid systems, and additive manufacturing further expand the versatility of this approach. Techniques such as 3D printing and continuous extrusion enable precise control over cube dimensions, porosity, and drug loading, supporting scalability and reproducibility within regulatory frameworks. As pharmaceutical development increasingly embraces precision engineering and patient-centric design, dissolution cube systems offer a promising frontier in oral drug delivery. Their ability to combine customizable geometry, tuneable release kinetics, and compatibility with advanced manufacturing technologies positions them as a next-generation platform capable of addressing complex solubility challenges while supporting personalized therapeutic strategies

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