

**Review article**

A comprehensive study on formulation and optimization of ivacaftor oral granules and determination of drug release by using USP-IV apparatus

Divyanshu Nagar*, Harshit Gautam

University Institute of Pharmaceutical Education & Research, University of Kota, Kota, Rajasthan, India

Corresponding author: Divyanshu Nagar, ✉ divyanshunagar4@gmail.com, **Orcid Id:** <https://orcid.org/0009-0003-2195-8269>

University Institute of Pharmaceutical Education & Research, University of Kota, Kota, Rajasthan, India

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Received - 30-6-2026, Revised - 22-07-2026, Accepted - 30-08-2026 (DD-MM-YYYY)

Refer This Article

Divyanshu Nagar, Harshit Gautam, 2026. A comprehensive study on formulation and optimization of ivacaftor oral granules and determination of drug release by using USP-IV apparatus. Journal of medical pharmaceutical and allied sciences, V 15, I 4, Pages 49 – 54. Doi: <https://doi.org/10.55522/jmpas.V15I4.7112>.

ABSTRACT

Ivacaftor is a first-in-class CFTR potentiator which has transformed the treatment of cystic fibrosis by targeting the underlying molecular defect rather than treating the symptoms alone. However, it is classified as a BCS Class II drug with poor aqueous solubility, which greatly limits its clinical utility. This review is directed toward the formulation challenges of ivacaftor, discusses the advanced solubility enhancement approaches such as solid dispersion techniques and discusses the application of USP Apparatus IV (flow-through cell) for biorelevant dissolution testing. The convergence of pediatric patient needs, regulatory requirements for generic formulations, and advances in technology provides a compelling reason to develop optimized oral granule formulations. This review provides a summary of the current literature concerning the physicochemical properties of ivacaftor, formulation strategies and dissolution methodology with special emphasis on the benefits offered by the USP-IV apparatus over conventional dissolution methods for poorly soluble drugs.

Keywords: Ivacaftor, Cystic fibrosis, Oral granules, USP-IV apparatus, Solid dispersion, Dissolution test, BCS class II, Solubility enhancement.

INTRODUCTION

Cystic fibrosis (CF) represents one of the most common life-threatening autosomal recessive disorders, primarily affecting populations of European descent. The condition arises from mutations in the gene encoding the cystic fibrosis transmembrane conductance regulator (CFTR) protein, an anion channel expressed at the apical plasma membrane of epithelial cells. The discovery and subsequent development of CFTR modulators—small molecules acting on the basic molecular defect in CF—have revolutionized the standard of care, drastically improving clinical features, prognosis, and quality of life.

Of these revolutionary therapies, ivacaftor is the first approved CFTR potentiator, a drug that increases chloride transport across epithelial membranes by opening the CFTR chloride channel. Four drugs with CFTR modulator activity are approved for clinical use to date, the potentiator ivacaftor alone or with correctors such as

lumacaftor, tezacaftor, and elexacaftor. Importantly, the triple combination therapy of ivacaftor, tezacaftor and elexacaftor is currently the most effective modulator therapy for the majority of people with CF and has recently received FDA approval for use in children as young as two years old.

Despite its clinical efficacy, ivacaftor poses major pharmaceutical challenges. The drug has practically no solubility (<0.001 mg/mL) over the pH range of 3.0 to 7.5, which leads to poor bioavailability after oral administration. Poor aqueous solubility, impacting about 40–70% of new drugs, causes low bioavailability and inconsistent therapeutic outcomes ^[1-4]. The present review critically discusses the literature on the physicochemical properties of ivacaftor, formulation approaches to improve its solubility, and USP Apparatus IV (flow-through cell) as an approach for biorelevant dissolution testing.

Ivacaftor: profile of a drug and pharmaceutical challenges

Physico-Chemical Property

Ivacaftor (C₂₄ H₂₈ N₂ O₃, molecular weight 392.49 g/mol) is a highly lipophilic compound with a log P of about 4.3. The drug is soluble in a pH-dependent manner and is essentially insoluble in the physiological pH range 3.0 to 7.5 [25]. In the Biopharmaceutics Classification System (BCS) (high permeability, low solubility), ivacaftor is classified as a Class II compound due to its poor aqueous solubility. Extensive first-pass metabolism of the drug occurs predominantly by CYP3A4/5 enzymes.

Biopharmaceutics Classification System as a scientific way to classify drugs based on their aqueous solubility and intestinal permeability.

For BCS Class II drugs like ivacaftor, dissolution becomes the rate-limiting step for absorption, making solubility enhancement a critical formulation objective [38].

Mechanism of action

A wide variety of CFTR mutations correlate to the cystic fibrosis phenotype and are associated with differing levels of disease severity. The most common mutation, affecting approximately 70% of patients with CF worldwide, is known as F508del-CFTR, in which a deletion in the amino acid phenylalanine at position 508 results in impaired production of the CFTR protein [20]. Ivacaftor as monotherapy has failed to show a benefit for patients with delta-F508 mutations, most likely due to an insufficient amount of protein available at the cell membrane for interaction and potentiation.

The next most common mutation, G551D, affecting 4-5% of CF patients worldwide, is characterized as a missense mutation, whereby there is sufficient protein at the cell surface, but channel opening and closing mechanisms are altered [9]. For this second type of mutation, ivacaftor is indicated to treat CF by binding to and enhancing the channel-opening ability of CFTR proteins present on the cell membrane [20].

Ivacaftor works as a potentiator of the CFTR protein, an ion channel involved in the transport of chloride and sodium ions across cell membranes of the lungs, pancreas and other organs. The overall level of ivacaftor-mediated CFTR chloride transport is dependent on the amount of CFTR protein at the cell surface and how responsive a particular mutant CFTR protein is to ivacaftor potentiation [21].

Clinical use and therapeutic landscape

Over the past decade, CFTR modulator therapy has evolved significantly. Following the success of ivacaftor monotherapy in patients with gating mutations, successive development of corrector drugs has enabled highly effective modulator therapy for more than 85% of the CF population over 12 years of age [30]. In >80% of individuals with CF, the triple combination of elexacaftor/tezacaftor/ivacaftor (ETI) has shown improved clinical outcomes, including sweat chloride and lung clearance index [26].

Ivacaftor is indicated for the treatment of cystic fibrosis in patients 2 months of age and older who have at least one mutation in the CFTR gene that is responsive to ivacaftor potentiation [9-22]. The common side effects of highly effective modulator therapies include cold-like symptoms, gastrointestinal symptoms, elevated liver enzymes and elevated creatine phosphokinase. Recent reports note potential neuropsychiatric effects requiring further investigation [26].

Commercial formulation: KALYDECO® (ivacaftor)

The reference listed drug, KALYDECO® (Vertex Pharmaceuticals), was approved by the FDA in 2012 as the first CFTR modulator therapy. The formulation strategy is based on polymeric amorphous solid dispersion to improve the solubility of the poorly water-soluble active pharmaceutical ingredient. The main excipients were microcrystalline cellulose and hydroxypropyl cellulose as a filler/binder, sodium lauryl sulfate as a surfactant to improve solubility, magnesium stearate as a lubricant, and titanium dioxide as a coating agent for UV stabilisation.

The choice of excipient is crucial to ivacaftor's bioavailability, stability and tolerability. Titanium dioxide acts as a UV stabilizer to prevent photodegradation of the API, while sodium lauryl sulfate and hydroxypropyl cellulose synergistically improve dissolution and absorption [23-28].

Ways to improve the solubility of ivacaftor

Techniques of solid dispersion

Solid dispersion is one of the most extensively studied approaches to increase the solubility of poorly water-soluble drugs. In this method, the drug is dispersed in a hydrophilic carrier, usually in an amorphous state with better dissolution properties [25].

Hot-melt extrusion (HME) has been successfully employed to prepare amorphous solid dispersions of ivacaftor. The research has shown that solid dispersions manufactured by HME with polymers such as Soluplus, Hypromellose 5 cps and Copovidone and surfactants such as sodium lauryl sulfate, poloxamer and polysorbate 80 increased the solubility greatly. Fourier-transform infrared spectrometry, X-ray diffraction, and differential scanning calorimetry confirmed the conversion of ivacaftor from crystalline structure form to amorphous structure form10. In vitro dissolution testing revealed a marked increase in dissolution rate of solid dispersions prepared by HME (95%) in optimized formulations compared to plain ivacaftor (9%) within 30 min [10].

The basic principles of solid dispersion technology are the formation of a molecular dispersion of drug within a polymer matrix. Understanding drug-polymer interactions and predicting storage stability are important aspects of phase diagrams as discussed in the literature. The glass transition temperature and drug solubility in the polymer are important parameters for the selection of processing conditions and levels of supersaturation [35].

Solubilization by surfactants

Surfactants are often used to increase the solubility of drugs which are poorly soluble in water by reducing interfacial tension and increasing wettability. The most frequently used surfactants in oral formulations are sodium lauryl sulfate and poloxamers [34].

A complex formulation, granulated, comprising copolymer of vinylpyrrolidone and vinyl acetate (Kollidon VA 64), poloxamer 338 (Pluronic F108) and sodium lauryl sulfate demonstrated a remarkable dissolution performance [6-10]. Comparative dissolution tests in water showed that the dissolution of ivacaftor from the granulated complex formulation was immediate with 90% of the ivacaftor dissolved within 10 min and 0% of the ivacaftor dissolved from the solid dispersion in 60 min. The complex had a minimum apparent solubility of 1 mg/mL in water and showed no observable food effect in beagle dog studies.

Nanodroplet formation and amorphous solid dispersions

Recent advances in understanding of drug-polymer interactions have shown the importance of amorphous phase separation and nanodroplet formation for enhanced drug solubility. Liquid-liquid phase separation has been shown to quantitatively enhance intestinal drug absorption of drug-rich nanodroplets. The solubility enhancement arises from the formation of drug-polymer nanodroplets and their morphology.

The generality of dissolution rate enhancement of free acid amorphous solid dispersions by sodium hydroxide has been demonstrated. These approaches are promising strategies to improve dissolution of poorly water-soluble drugs such as ivacaftor.

Quality by design (QbD) in the development of formulations

Pharmaceutical companies have applied Quality by Design principles to product development and process understanding. The QbD application in the development of lumacaftor/ivacaftor fixed-dose combination granules illustrates the value of systematic product and process development [31]. Spaces have been designed for the design of processes of manufacturing granules and substantiated with appropriate in-process controls to ensure the reproducible quality of the product.

Oral granules: a versatile drug delivery system

Oral granules are becoming an important dosage form, especially for pediatric and geriatric patients. Granules have several advantages such as improved flow properties, better content uniformity, improved dissolution and flexible dosing [11].

Ivacaftor is already available in oral granule formulations for pediatric use, as evidenced by the lumacaftor/ivacaftor fixed-dose combination granules for patients aged 2 to <6 years [31]. The process of granule production includes the blending of the active substance with intragranular excipients, granulation, drying, milling, and packing into sachets.

Common granulation techniques used in pharmaceutical manufacturing are wet granulation and melt granulation. Wet granulation improves the cohesion of powders and provides uniform distribution of drugs which is important to ensure consistent drug release. It is reported that the selection of appropriate excipients, binders and disintegrants is a key factor affecting the quality and performance of granules. Improved wettability can further facilitate the dissolution of surfactants and hydrophilic polymers.

Dissolution testing and the USP apparatus IV

Significance of dissolution testing

Dissolution testing is an important part of the evaluation of the performance of oral dosage forms. Information on drug release behavior is obtained, and the in vivo performance can be predicted [14, 15]. In dissolution testing of poorly soluble drugs like ivacaftor, the main challenges are to maintain sink conditions and prevent drug precipitation.

USP-IV apparatus: design and operation

The United States Pharmacopeia (USP) Apparatus IV, or flow-through cell apparatus, is an advanced dissolution testing system that is fundamentally different from the traditional USP Apparatus I (basket) and II (paddle) methods. A pump drives dissolution media up through a vertical flow-through cell which has a reservoir system and filter system to trap undissolved particles [24, 29].

Key features of the operation include

Flow-through design: The test sample is placed in a cell through which the dissolution medium is continuously flowing.

CONTROL OF TEMPERATURE: Precisely maintained at 37°C ± 0.5°C.

Cell Sizes: Available in 12 mm and 22.6 mm diameter configurations.

Flow rates: Usually 4, 8, or 16 mL/min, depending on the application.

Configurations: open-loop (continuous supply of fresh media) or closed-loop (media recirculation).

It is a specifically designed apparatus for powders, microparticles, pellets, implants, suppositories and tablets and therefore well suited for the examination of granular formulations. The use of USP-IV has been shown to increase the prediction of drug behaviour in vivo and to create an in vitro-in vivo correlation (IVIVC).

Advantages of conventional dissolution apparatus

The USP-IV apparatus has unique advantages in several aspects, making it particularly useful for evaluation of poorly soluble drugs such as ivacaftor:

Maintenance of Sink Conditions: This flow-through design can provide fresh media continuously, while the volume of the dissolution medium in USP-I/II apparatus is fixed, maintaining true sink conditions throughout the test duration. This is important for

drugs with poor solubility where saturation can occur rapidly in conventional equipment.

Biorelevant media compatibility – The system allows sequential testing in different biorelevant media simulating gastrointestinal transit. Researchers can program media changes from fasted state simulated gastric fluid (FaSSGF, pH 1.2) to fasted state simulated intestinal fluid (FaSSIF, pH 6.5) to fed state simulated intestinal fluid (FeSSIF, pH 5.0), simulating the changing environment of the gastrointestinal tract.

Hydrodynamic Benefits: The problems of the traditional paddle/basket apparatus are coning (undissolved particles accumulating at the bottom of the vessel), variability of hydrodynamics and poor discrimination for fine particles. The USP-IV's laminar flow circumvents these problems and is particularly useful for drugs with small particle size and large surface area that dissolve at a faster rate than in other compendial apparatuses.

Flexibility for New Formulations: The flow-through cell can be adapted to various dosage forms including powders, implants, suppositories and controlled release formulations. This versatility is critical for the evaluation of granular formulations [30].

***In Vitro* – *In Vivo* correlation (IVIVC)**

IVIVC is an important tool in pharmaceutical development, correlating in vitro drug release data with in vivo pharmacokinetic parameters. For BCS Class II drugs, dissolution is the rate-limiting step, so IVIVC is very important. Conventional methods have been demonstrated to have worse correlation to in vivo data than enhanced dissolution methods such as USP-IV. Better IVIVC reduces the need of extensive clinical studies and facilitates regulatory approval.

Research issues and prospects

Despite numerous studies on the solubility enhancement of ivacaftor, the following gaps still exist:

Lack of studies on optimization of oral granule formulation. Although solid dispersion techniques have been studied extensively, systematic optimization of ivacaftor granule formulation has not been investigated so far.

USP-IV apparatus-based limited evaluation: The majority of the dissolution studies of ivacaftor have been carried out using standard USP-I and II apparatus. There has not been extensive study on the use of USP-IV for the evaluation of ivacaftor granules.

Limited IVIVC of granule formulations: Reliable IVIVC of granule formulations for poorly soluble drugs remains a challenge.

Integration of formulation optimization with advanced dissolution testing. Most studies have dealt with individual techniques rather than integration of formulation optimization with biorelevant dissolution testing.

Formulation considerations for pediatrics. Oral granules are a suitable dosage form for pediatric patients; however, the

formulation challenges include taste masking, dosing flexibility and patient acceptability.

CONCLUSION

The literature clearly reveals the clinical significance of ivacaftor in CF therapy and the great formulation challenges due to poor aqueous solubility. Hot-melt extrusion, a solid dispersion technology, has demonstrated exceptional success in improving ivacaftor dissolution, with >95% release compared to 9% for pure drug. The USP-IV flow-through cell apparatus offers clear advantages over traditional dissolution methods for the assessment of such poorly soluble drugs, including the preservation of sink conditions, compatibility with biorelevant media and improved hydrodynamic properties.

The needs of pediatric patients, the regulatory requirements for generic products and the advances in formulation technology converge to provide a strong rationale for the development of optimized ivacaftor oral granules. Systematic optimization of ivacaftor oral granules using USP-IV dissolution testing represents a valuable addition to the literature that may have implications for improving CF therapy for vulnerable patient populations.

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