Journal of Molecular Science

Journal of Molecular Science
Volume 35 Issue 3, Year of Publication 2025, Page 752-761
DoI-10.004687/1000-9035.2025.102

Journal of Molecular Science
www.jmolecularsci.com ISSN:1000-9035

Molecular Insights and Formulation Strategies in Co-Crystallization of BCS Class III and IV Drugs: Bridging Solubility and Permeability Gaps: A Comprehensive Review

Ms. Rutuja Ramesh Gharal[1*], Mr. Prathmesh Dadaso Patil[2], Mr. Kalleshvar P. Jatte[3], Ms. Komal Sunil Pol[4], Mrs. Monali Dipak Jadhav[5]

[1-2]Department- Pharmaceutics, Krishna Institute of Pharmacy, Krishna Vishwa Vidyapeeth, Deemed to be University, Karad, 415110

[3]Department of Pharmaceutical Chemistry, Dinesh Bembade College of Pharmacy, Mahalangra. Tq- Chakur, Dist –Latur, 413513

[4]Department of Pharmaceutical Chemistry, Krishna Charitable Trust's, Krishna College of Pharmacy, Tal Karad; Dist. Satara, 415111

[5]Department of Pharmaceutical Chemistry, Krishna Institute of Pharmacy, Krishna Vishwa Vidyapeeth, Deemed to be University, Karad, 415110.

Article Information
Received: 16-09-2025
Revised: 05-10-2025
Accepted: 22-10-2025
Published: 14-11-2025

Keywords
Co-crystallization, BCS classification, Drug permeability, In vitro In vivo correlation

ABSTRACT

Enhancing the solubility and permeability of drugs classified under Biopharmaceutics Classification System (BCS) classes 3 and 4 is crucial for improving their bioavailability and therapeutic efficacy. These classes encompass drugs with challenges such as high solubility and low permeability (class 3) or low solubility and permeability (class 4), posing significant formulation hurdles. Co-crystallization emerges as a promising strategy to address these challenges by altering the crystalline structure of drug molecules through interactions with suitable co-formers. Co-crystallization involves the combination of drug molecules with co-formers that can form hydrogen bonds or other interactions, leading to the formation of new crystalline forms. This method aims to optimize dissolution properties and enhance permeation across biological barriers, thereby improving drug absorption and effectiveness. By strategically selecting co-formers and optimizing crystallization conditions, researchers can tailor drug formulations to maximize solubility and permeability.

The application of co-crystallization in pharmaceutical development not only enhances drug performance but also aligns with Quality by Design (QbD) principles, facilitating efficient formulation design and regulatory approval. Understanding and manipulating crystalline forms through co-crystallization offer a pathway to overcoming inherent limitations of BCS class 3 and 4 drugs, ultimately advancing patient outcomes in clinical settings.

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INTRODUCTION:

OVERVIEW OF BCS CLASSIFICATION:

The most important characteristics of drugs is their solubility which means the capacity to dissolve in a particular type of solvent and prepare a homogeneous mixture. The different factors that affect solubility of drug solvents, temperature and pressure of different variables. The rates of mass transfer across intestinal membrane and the absorption of pharmacological compounds in people are classified according of the limits of Permeability.[1]

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Biopharmaceutics classification system (BCS) has an wide use for drug discovery and development. BCS classification is classified according to intestinal permeability and solubility. This classification helps to identify the oral absorption and intestinal permeability and accordingly can be put into the specified class.[2]

BCS CLASSIFICATION:

Class I: HIGH SOLUBILITY AND HIGH PERMEABILITY

The drugs in this class are very well absorbed and have high bioavailability. They pass through intestinal membranes with ease and disintegrate easily in gastrointestinal fluids.

Class II: HIGH PERMEABILITY AND LOW SOLUBILTY

The drugs in this class are not soluble in GIT fluids, they pass through intestinal membrane with ease and have high permeability.

Class III: HIGH SOLUBILITY AND LOW PERMEABILITY

This drugs are highly soluble but have poorly permeability across intestinal membranes. Permeability usually affects the absorption instead disintegration rates.

Class IV: LOW SOLUBILITY AND LOW PERMEABILITY

These drugs have trouble passing through intestinal membranes and are poorly soluble in gastrointestinal fluids. They have decreased bioavailability due to poor permeability of drugs.[3]

SIGNIFICANCE OF CLASS 3:

Pharmaceuticals drugs of BCS class 3 have high permeability and low solubility. These drugs have difficulties in dissolving but have effective membrane transport. Mostly this class stimulates improvement in formulation with the aim to improve the solubility of drug to increase its bioavailability. The formulation strategies aim to enhance the permeability of drug typically through techniques like Prodrug design, Lipid - lipid based formulation or Particle size reduction. These methods are helping to close the gap between formulation science and legal requirements, which improves patient outcomes and therapeutic efficacy in the end. A significant role is played by BCS class 3 compounds in the end.[2]

SIGNIFICANCE OF BCS CLASS 4:

Pharmaceutical drugs of BCS class 4 have low solubility and low permeability, which shows a serious challenge in both I dissolving the drug in GI fluids and crossing the Intestinal membrane leading to poor drug absorption and low bioavailability. Some problems like low aqueous solubility, poor permeability, erratic and poor absorption can also be seen. And to solve these trouble some of the techniques are in work such as Lipid based delivery systems, Polymer based nanocarriers, Micro-ionization, or Complexation to improve solubility and enhance bioavailability of drugs. All the formulation methods are focusing to improve both solubility as well as permeability to enhance absorption of drug. To control these challenges often requires innovative approaches towards each drugs properties. By addressing the limitation related to BCS class 4 drug can lead to improved therapeutic outcome like expanded patient access and enhanced commercial viability for pharmaceutical products.[4]

IMPORTANCE OF ENCHANCEMENT OF DRUG PERMEABILITY

1. DRUG ABSORPTION:

The drugs with low permeability, this is especially crucial in order to guarantee sufficient bioavailability and therapeutic efficacy. Improving permeability to pass through biological barriers GIT and blood brain barriers increases the amount of drug absorbed into systemic circulation.

2.THERAPEUTIC INDEX:

The drugs having less or inadequate permeability of several medications with encouraging pharmacological effect may have restricted bioavailability.

3.OPTIMISED FORMULATION STRATEGIES:

The different delivery methods for suitable drugs and their intended routes of administration is enhanced by permeability enhancement which directs the formulation efforts.

4.IMPROVED PATIENT COMPLAINCE:

Reduced dosage forms due permeability enhancement of drug which increases the patient compliance as well. This is an important factor which is considered in long term disease conditions.[7]

OBJECTIVE OF THE REVIEW:

1. Increase the absorption and bio-availability of BCS class 3 and class 4 drugs the more soluble drug across biological barriers and GI fluids. This may accelerate the methods to improve drug absorption by increasing membrane permeability.
2.improve the percentage of drug bioavailability which enters into the systemic circulation by enhancing drug permeability.

3.To reduce past obstacles to absorption optimized formulation methods can be used. Increase

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solubility, enhance drug permeability or protect it from GIT fluids.
4.maximized therapeutic efficacy is depended on higher medication plasma level concentrations can be the consequences of enhanced permeability which increases therapeutic efficacy.
5.Reduced variability due inconsistent therapeutic effects because of improper drug absorption. Researchers are trying to reduce the variability and provide consistent plasma level concentration of drug in blood.
6.To prepare innovative delivery systems to enhance drug solubility and permeability like micelles, liposomes, nanoparticles, and other carriers.
7. Researching permeation enhancement imposes lights on the mechanisms of drug transport across membranes and absorption. Designing permeation enhancement methods that are more effective can be guided by an understanding of these mechanisms.
8.Adherence to regulatory requirements. While assessing bio equivalency and licensing of drug formulations, the permeability and solubility is considered on high account.
9. Effects of Drugs may have non specificity due to their physical characteristics due to particular molecular interactions that can be maintained.[5]
Overview of drug permeability and different mechanism and constraints (at molecular level) with diagrammatic representation:

MECHANISMS TO INCREASE DRUG PERMEABILITY:

Prodrug Approach: Prodrug approach is a chemical modification of a drug molecule to increase its membrane permeability and solubility. Prodrugs are can undergo biotransformation into the active drug form after crossing the membrane.

Nanotechnology: By utilizing nanoparticles to encapsulate the drugs can enhance their permeability by shielding them from degradation and facilitating transport across biological membranes.[7]

Use of Penetration Enhancers: few compounds which are known as penetration enhancers can change the integrity of the biological membranes, by enhancing drug permeability. Examples include Surfactants, Fatty acids, and Bile salts formulations.

Lipid-Based Formulations: By Formulating drugs in lipid-based carriers, like liposomes and lipid nanoparticles may enhance the solubility and permeability of drugs.[9]
Targeting Transporter Proteins: Design of drugs that specifically target transporter proteins responsible for drug uptake or efflux can increase their permeability across intestinal membrane.
pH Modification**:** By Modifying the pH of internal environment, such as using pH-modified formulations or alkalizing agents, can optimize drug ionization and enhance permeability in specific biological departments.[8]

METHODS OF PERMEABILITY STUDIES:
A) IN VITRO CELL CULTURE MODELS:
1.TRANWELL ASSAY
During this assay, endothelial cells are placed on the upper layer of a cell culture insert with permeable membrane and a solution containing the test agent is placed below the cell permeable membrane. Following an incubation period (3–18 hours), the cells that have migrated through the membrane are stained and counted. The membrane is usually coated with some extracellular matrix component (e.g. collagen) which facilitates both adherence and migration.[4]

2. CACO -2 CELL MONOLAYER:
Human colon adenocarcinoma is used as it resembles the intestinal epithelium. the transport of drugs from the apical side to the basolateral side or vice versa is measured. In order to evaluate absorption of compounds across the membrane via a transcellular route, the permeability of peptide derivatives. and related compounds. was measured by the parallel artificial membrane permeation assay (PAMPA).[3] The permeability coefficient by PAMPA were analysed quantitatively. using classical QSAR and Volsurf approaches with the physicochemical parameters. The results from both approaches showed that hydrogen bonding ability of molecules in addition to hydrophobicity at a particular pH were significant in determining variations in PAMPA permeability coefficient. The relationship between Caco-2 cell permeability and artificial lipid membrane permeability was then determined. The compounds were sorted according to their absorption pathway in the plot of the Caco-2 cell and PAMPA permeability coefficient.[6]

B) EX VIVO TISSUE MODELS:
1.USING CHAMBERS:
Samples such as intestinal membrane or skin tissues are mounted between two compartments. The measurement of drug transport from one side to other side is measured under controlled conditions. Electrodes are often used to monitor changes in electrical resistance.[5]

2.ISOLATED ORGAN PERFUSION:
Isolation and perfusion of organs like liver and intestine are done in drug solution. The concentration of the drug in the perfusate and

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tissues is monitored to estimate permeability of drug.[7]

C)IN SILICO METHOD:
1.VIRTUAL SCREENING:
The different molecular dynamics simulations and quantitative structure activity relationship (QSAR) models are used in studying the drug permeability. It is widely recognized that adsorption, distribution, metabolism, excretion, and toxicology liabilities kill the majority of drug candidates that progress to clinical trials. The development of computational models to predict small molecule membrane permeability is therefore of considerable scientific and public health interest.[8]

D) IN VIVO ANIMAL MODELS:
1.ANIMAL MODELS:
The drug is administered in rodents via different routes of administration samples of blood and tissue samples are taken at different point of time to measure drug concentration and assess permeability.

2.PERMEABILITY IMAGING:
Techniques like (PET) positron emission tomography or (MRI) Magnetic resonance imaging combined with contrast agents can be used to visualize and quantify drug distribution and permeability.

E) HUMAN STUDIES:
1.PHARMACOKINETIC STUDIES:
Pharmacokinetic parameters such as area under the curve (AUC) and bioavailability are determined to assess drug permeability in clinical trials of new drug discovery.+

F) ARTIFICIAL MEMBRANE MODEL:
1.THE PARALLEL ARTIFICIAL MEMBRANE PERMEABILITY ASSAY:
PAMPA involves the use of an artificial lipid membrane that mimics the phospholipid bilayer of biological cell membranes. The assay measures the rate at which a drug diffuses from a donor compartment through the artificial membrane into an acceptor compartment.

PAMPA is a valuable tool in drug development for evaluating the passive permeability of compounds. Its high throughput and cost-effectiveness make it an attractive option for early-stage screening, although it should be complemented with other assays to obtain a comprehensive understanding of a drug's permeability characteristics.[4]

4.CO-CRYSTALLIZATION TECHNIQUES AND CHARACTERIZATION :-

4.1FUNDAMENTALS AND PRINCIPLE: -
Co-crystallization is a process used in pharmaceutical development and materials science to create new solid forms by combining an active pharmaceutical ingredient (API) with a co-former, resulting in a stable crystal lattice. This technique relies on non-covalent interactions such as hydrogen bonding, van der Waals forces, and π-π interactions to form a unique crystalline structure without altering the chemical composition of the API.[7]

Co-crystals, a class of crystalline materials composed of two or more components, have gained attention in sustainable and green research due to their potential for enhancing drug delivery systems. By utilizing eco-friendly solvent systems and renewable starting materials, researchers are developing environmentally benign synthesis methods for co-crystal pro duction. These sustainable approaches not only minimize the environmental impact but also promote the development of greener pharmaceuticals with improved solubility and bioavailability.[9] Numerous numbers of active pharmaceuticals (APIs) with limited aqueous solubility have been found in recent years. About 60%–70% of the molecules in these recently found medications belong to BCS classes II and IV. The reduced water solubility of APIs, which results in low bioavailability of medications, has prevented the development of several APIs in formulations Because the pH of the gastrointestinal tract varies depending on the region, drugs administered orally have varying solubilities in gastrointestinal fluids at varying pHs, which frequently results in nonlinear and variable absorption and makes it difficult to assess the efficacy and safety of medications. Because of this, creating oral dosage forms is a significant problem due to the low solubility of medicines.[6] To increase a drug's solubility and increase its bioavailability, researchers have developed several strategies. Some methods are used to increase the solubility of weakly water-soluble pharmaceuticals. Each methodology has advantages and disadvantages, and when choosing a technique, it is important to consider elements like the qualities of the active pharmaceutical ingredient (API), the nature of the chosen excipients, the process of development, and the nature of the dosage form.[5]

Co-crystallization exploits the interactions between different molecules to create a stable and organized crystal lattice. The main interactions include:
Hydrogen Bonding: Strong directional interactions between a hydrogen atom and electronegative atoms (e.g., oxygen, nitrogen).

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Van der Waals Forces: Weak, non-directional forces arising from temporary dipoles in molecules.
π-π Interactions: Interactions between aromatic rings that contribute to the stability of the crystal lattice.[2]

Benefits of Co-Crystallization:
Co-crystallization addresses several physical property issues in pharmaceutical development:
Solubility: Improves the solubility of poorly soluble APIs, enhancing their bioavailability.
Stability: Increases the chemical and physical stability of the API.

Bioavailability: Enhances the absorption and efficacy of the drug.[4]

CHALLENGES AND LIMITATIONS
CHALLENGES:
1. Solubility Differences: Co-formers and APIs often have different solubilities, which can complicate the co-crystallization process. Finding conditions where both components remain in solution and then crystallize together can be challenging.
2. Stoichiometry Control: Achieving the desired stoichiometry in the co-crystal can be difficult. Controlling the ratio of the co-former to the API is crucial for obtaining the desired properties of the co-crystal.
3. Polymorphism: Co-crystallization may lead to the formation of multiple polymorphic forms, each with different properties. Identifying and characterizing these polymorphs is essential but can be time-consuming and require specialized techniques.
4.Structural Stability: Ensuring the stability of the co-crystal structure under various environmental conditions (e.g., temperature, humidity) is vital for its pharmaceutical application. Structural changes or decomposition can affect the efficacy and safety of the co-crystal product.[2]

LIMITATIONS:
1. Predictability: It can be difficult to predict the outcome of co-crystallization due to the complex interactions between the co-former and the active pharmaceutical ingredient (API). Factors like solvent choice, stoichiometry, and temperature can all affect the outcome.
2. Screening Challenges: Not all molecules readily form co-crystals. Screening for suitable co-formers can be time-consuming and may require extensive experimentation.
3. Limited Improvement: Co-crystallization may not always lead to significant improvements in the properties of the API. For example, while it may enhance solubility or stability in some cases, it may not have a noticeable effect in others.
4. Scale-up Issues: Transitioning from laboratory-scale co-crystallization to large-scale production can be challenging. Factors like reproducibility, scalability, and cost-effectiveness need to be carefully considered.[5]

CHARACTERIZATION ANALYTICAL TECHNIQUES:
1. X-ray diffraction (XRD): XRD is a widely used, accurate technique for co-crystal identification and qualification. Large-size crystals that are often generated by solvent evaporation technique are typically structurally identified using single-crystal XRD. Single-crystal XRD is unable to characterize the co-crystal that was produced during grinding.[7] Because of this, the primary use of PXRD technology is the identification of co-crystal formation. Co-crystals in PXRD exhibit different characterisation peaks from their component co-crystals. The percentage of co-crystals and co-crystal components in the final product are quantified using XRD techniques to determine the co-crystal yield percentage.[9]

2.Thermal analysis method:
There are primarily two techniques available for characterizing co-crystals in thermal analysis.[2]

3.DSC differential scanning calorimetry:
Characterizing co-crystals is made simple and convenient by differential scanning calorimetry. When comparing the endothermic and exothermic peaks of co-crystals to those of pure components, a notable shift is seen. By looking at the DSC peak of the physical mixture of co-crystal components, one can screen for co-crystals by locating the co-crystal DSC peak, which is located between the peaks of pure co-crystal component DSC peaks.[8] But there are several examples of co-crystals that have been prepared such that the DSC peaks are outside the range of the co-former and API. This implies that the previously stated rule cannot be applied universally to the conformation of co-crystal formation. DSC is an incredibly quick and effective way to characterize co-crystals.[3]

4.HSM hot stage microscopy
Co-crystal characterisation and screening are two of HSM's most well-known applications. With HSM, users can see how the melted co-crystal components expand and recrystallize. Kofler mixed fusion method can be used for co-crystal characterization and screening. This technique shows the crystalline material at the interface between two components, which raises the probability of co-crystal formation between co-crystal components.[7]

5.Analysis via Spectroscopy

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There are two primary categories for co-crystal spectroscopic characterization. Nuclear magnetic resonance spectroscopy is the second method, whereas vibrational spectroscopy is the first. FTIR and Raman spectroscopies are two subsets of the vibrational spectroscopic approach. Raman spectroscopy studies the scattering process of spectroscopy, while infrared spectroscopy studies the absorption mechanism. A highly effective technique for obtaining comprehensive structural data about multi-component systems is NMR spectroscopy.[4]

6. Fourier transform infrared spectroscopy

FTIR spectroscopy is a very efficient tool to identify the formation of co-crystals. The formation of co-crystals is confirmed by a change in vibrational energy peaks in spectra, mainly due to the formation of hydrogen bonding in the functional group of co-crystal components. FTIR spectra of pure co-crystal components and formulated co-crystals are compared for detection of co-crystal formation and structural elucidation.[9]

7.Raman spectroscopy

Raman spectroscopy is an in-situ monitoring and characterization method for co-crystal formation confirmation. Raman spectroscopy exhibits better accuracy, precision, and sensitivity than the FTIR method. Raman spectroscopy can differentiate between co-crystal form and ionic form of multi-component systems. Evaluation of the formation of co-crystals is done by comparing the change in the oscillation of co-crystals in comparison to co-crystal components.[7]

8.Solid-state NMR spectroscopy

SSNMR has the potential to provide detailed structural information about organic and pharmaceutical co-crystals. SSNMR provides higher information content and high-yield data as compared to vibrational spectroscopy and PXRD methods. SSNMR is a non-destructive method and requires a very small number of samples for data collection.[8]

7.PERMEABILITY ENCHANCEMENT IN VIVO IN VITRO CORRELATION CONSIDERATIONS:

In vitro–in vivo correlations (IVIVCs) of oral solid products have received considerable attention from the industry, regulatory agencies, and academia over the previous years. Defining a quantitative and reliable relationship between *in vitro* drug release and *in vivo* absorption is highly desired for rational development, optimization, and evaluation of solid dosage forms and manufacturing process.[6]

A validated IVIVC can significantly increase the development efficiency by reducing the time, and resources required for formulation and process development, scale-up, and optimization, and it also ensures product quality by setting meaningful specifications.

In developing an IVIVC, the *in vitro* parameters commonly utilized are the amounts of drug released that can be determined with precision under controlled conditions.[4]

For test formulations that exhibit varying apparent *in vivo* absorption characteristics, the most critical element in establishing an IVIVC is the ability of *in vitro* tests to correlate quantitatively with *in vivo* performance.

The essential conditions for developing an IVIVC include: the apparent *in vivo* absorption is dissolution rate limited; *in vitro* dissolution and/or erosion is the critical dosage form attribute; test formulations exhibit different *in vivo* performance; and the *in vitro* test is discriminating (IVIVR) and/or predictive (IVIVC).[3]

BCS CLASS 3 DRUGS:

Sr.no.	Name of drug	Method of co-crystallization	Co-former	Initial solubility	Final solubility	Initial permeability	Final permeability	Initial bioavailability	Final bioavailability
1.	5-fluoro uracil (Anti-cancer)	Solvent evaporation And Liquid phase assisted grinding	3-hydro-benzoic acid 4-amino benzoic acid Cinnamic acid	12.2 mg/ml	No remarkable impact on Cs. No remarkable impact on Cs. No remarkable impact on Cs.	Log p= -0.89	1.4 -fold higher stead penetrate rate. 1.6-fold higher stead penetrate rate. 1.-fold higher stead penetrate rate.	>10%	
Reference- https://bi.tbzmed.ac.ir/FullHtml/bi-17553									

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Sr. no	Name of drug	Method of co-crystallization	Co-former	Initial solubility	Final solubility	Initial permeability	Final permeability	Initial bioavailability	Final bioavailability
2.	Pyrazinamide (Anti – tubercular)	Solvent Evaporation And Anti solvent method	Malonic Acid Glutaric Acid Succinic Acid Adipic Acid Sebacic acid Trans-Aconitic acid Citric acid 2,4 dihydro benzoic acid 2,6 dihydro benzoic acid 3,5 dihydro benzoic acid	22mg/ml	66.5 mg\ml 49.7 mg\ml 37.2 mg\ml 12.57 mg\ml 12.54 mg\ml 30.60 mg\ml 21.05 mg\ml 7.07 mg\ml 12.18 mg\ml 24.26 mg \ml	10^-6 – 10^-5 cm/s	1.4-fold higher stead penetrate rate. 1.6-fold higher stead penetrate rate. 1.-fold higher stead penetraterate.	70-90%	
Reference- **https://www.sciencedirect.com/science/article/pii/S0022286018306720**									

Sr. no	Name of drug	Method of co-crystallization	Co-former	Initial solubility	Final solubility	Initial permeability	Final permeability	Initial bioavailability	Final bioavailability
3.	Adefovir (Anti – retroviral or Anti-viral)	Liquid-assisted grinding	Stearic acid	1mg/ml Or less	Enhanced	10^-6	No remarkable impact on the apical to basal transport rate	59%	
Reference- **https://bi.tbzmed.ac.ir/FullHtml/bi-17553**									

Sr. no.	Name of drug	Method of co-crystallization	Co-former	Initial solubility	Final solubility	Initial permeability	Final permeability	Initial bioavailability	Final bioavailability
4.	Isoniaz	Anti solvent		137.96		1.8±0.1cm/s	Final	90-100%	

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	id (Anti - tubular)	crystallization	Oxalic acid Malic acid Methane sulfonic acid	mg\ml	5.43 mg\ml 403.95 mg\ml 485.91 mg\ml		permeability		
Reference- **https://www.sciencedirect.com/science/article/pii/S0022286018306720**									

Sr. no.	**Name of drug**	**Method of co-crystallization**	**Co-former**	**Initial solubility**	**Final solubility**	**Initial permeability**	**Final permeability**	**Initial bioavailability**	**Final bioavailability**
5.	Acyclovir (Anti – viral)	Co-crystallization included griding with drop wise solvent addition and solvent evaporation.	Fumaric acid Glutaric acid	Approx 0.2mg/ml Or 1.2 – 1.6mg/ml	1.53-fold higher apparent Cs 2.14-fold higher apparent Cs	1-2* 10^-6 cm/s	2.8-fold higher permeated amount. 4-folds higher permeated amount	10-20%	
Reference- **https://bi.tbzmed.ac.ir/FullHtml/bi-17553**									

Sr. no.	**Name of drug**	**Method of co-crystallization**	**Co-former**	**Initial solubility**	**Final solubility**	**Initial permeability**	**Final permeability**	**Initial bioavailability**	**Final bioavailability**
6.	**Furosemide (Diuretic)**	**Solvent evaporation And Liquid assisted grinding.**	**Anthranilamide** **Caffeine** **Adenine** **TMP** **Imidazole** **5-fluorouracil**	**0.081mg\ml**	**Higher Cs** **Lower apparent Cs** **No remarkable impact on Cs** **Higher apparent Cs** **9.61 (× 118.7)** **0.22× (2.7)**	**0.11×10^-6 cm/s**	**Higer cumulative permeated amount\ flux** **Lower cumulative permeated amount \ flux** **Higher cumulative permeated amount\flux** **Higher cumulative permeated amount\ flux** **0.304 ± 0.018×10^-6 cm/s** **0.224 ± 0.005×10^-6 cm/s**	**50%**	**37-51%**
Reference- **https://bi.tbzmed.ac.ir/FullHtml/bi-17553**									

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Sr.no.	Name of drug	Method of co-crystallization	Co-former	Initial solubility	Final solubility	Initial permeability	Final permeability	Initial bioavailability	Final bioavailability
7.	HCTZ (Hydrochloro-thiazide (Diuretic)	Liquid assisted method	Piperazine TMP Picolinamide Isoniazid Malonamide Nicotinic acid Nicotinamide 4-aminobenzoic acid Succinimide Resorcinol	722 mg\ml	6.6-folds higher apparent Cs No remarkable impact on Cs 3-folds higher apparent Cs No remarkable impact on Cs No remarkable impact on Cs \ 1.4- fold lower apparent Cs 1.3-fold higher apparent Cs 2.4-fold higher apparent Cs 4.7- fold lower apparent Cs 2.4-fold increase in Cs	10 ^-6 cm/s	Higher cumulative permeated amount\ flux Lower cumulative permeated amount\ flux Higher cumulative amount\ flux Higher cumulative amount\ flux Higher cumulative amount\ flux 2-fold higher permeability 1.8-folf higher permeability 1.3-fold higher permeability Lower permeability 1.6-fold higher permeability	80%	
Reference- **https://bi.tbzmed.ac.ir/FullHtml/bi-17553**									

Sr. no.	Name of drug	Method of co-crystallization	Co-former	Initial solubility	Final solubility	Initial permeability	Final permeability	Initial bioavailability	Final bioavailability
8.	Chlorthalidone (Diure	Solid-state grinding	Caffeine	0.27mg/ml	2 ± 0.03 mg\ml	No specific values	No specific values.	64%	

	tic)								
Reference- **https://www.mdpi.com/1999-4923/14/2/334**									

Sr. no.	**Name of drug**	**Method of co-crystallization**	**Co-former**	**Initial solubility**	**Final solubility**	**Initial permeability**	**Final permeability**	**Initial bioavailability**	**Final bioavailability**
9.	Ciprofloxacin	Liquid-assisted grinding technique	Nicotinic acid Iso-nicotinic acid	36 mg/ml	Twenty-fold increased Twenty-fold increased	1*10^-5 To 2*10^-5 cm/s	1×10^-5 to 2×10^-5 cm/s	70 To 80%	
Reference- **https://www.sciencedirect.com/science/article/pii/S0040603119304496**									

CONCLUSION:

After carrying out comparative studies of BCS class 3 and class 4 drugs by method of co-crystallization we can conclude that, the Biopharmaceutics Classification System (BCS) is a crucial tool in drug development, significantly aiding in the understanding and improvement of drug solubility and permeability, which are key determinants of oral absorption and bioavailability. By addressing the limitations associated with BCS Classes III and IV drugs through innovative formulation techniques and permeability enhancement strategies, researchers and pharmaceutical developers observed that there is a significant improvement in drug absorption, bioavailability, and therapeutic efficacy, ultimately leading to better patient outcomes and enhanced commercial viability for pharmaceutical products.

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