International Journal of Research in Pharmacy and Pharmaceutical Sciences
www.pharmacyjournal.in
ISSN: 2455-698X
Received: 14-09-2025, Accepted: 13-10-2025, Published: 29-10-2025
Volume 10, Issue 4, 2025, Page No. 33-36

Technique for enhancing the Permeability & oral Bioavailability profile of Carbapenem

K Shanthini, Samrin Nifana A, Sandhiya U, Ushman Shalima KA, Vengat Vishal S
Assistant Professor, Students, Department of Pharmaceutics, RVS College Of Pharmaceutical Sciences, Sulur, Coimbatore, Tamil Nadu, India

Abstract
Carbapenems are beta-lactam antimicrobial agent with broad spectrum activity. Carbapenem falls under class III BCS classification based on high solubility and low permeability. Carbapenem has a basic structure on 1, azabicyclo [3, 2, and 0] hept-2-ene-2-carboxylic acid. In this review, we summarize the technique for enhancing the permeability and oral bioavailability profile of carbapenem. The techniques include Prodrug formulation, Drug as transport protein inhibitors, Pharmaceutical excipients as transport protein inhibitors, polymeric and lipid based nanocarriers utilized for the delivery of anti-microbial agents. This includes indications and adverse effect of carbapenem. In closing with marketely available and non available formulation of Carbapenem and its derivatives.

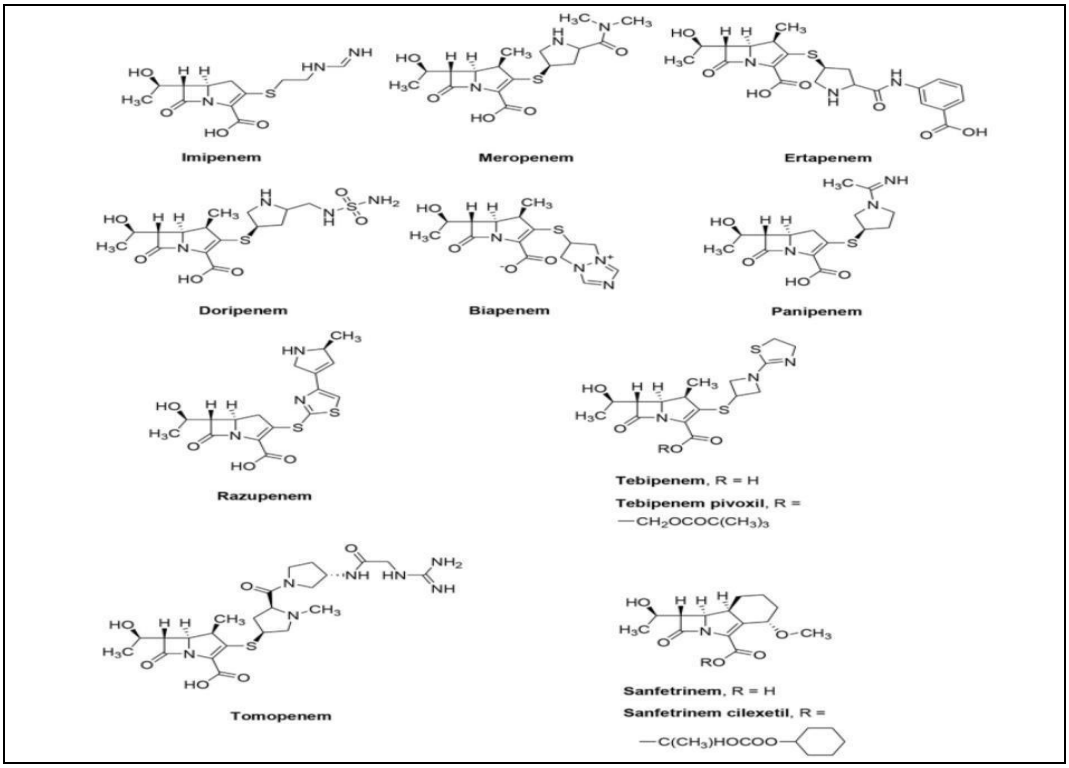
Keywords: Carbapenem, antibiotic, enhancing technique, permeability enhancement, formulation, intravenous administration

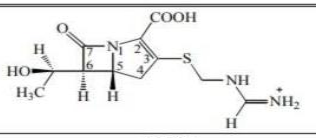
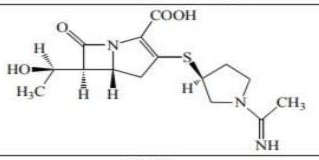
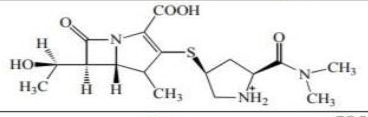
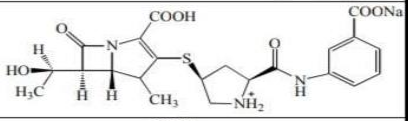
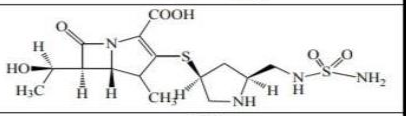
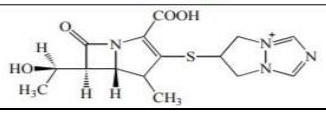
Introduction

Carbapenems are beta-lactam antibiotics that work against a wide variety of infections. They are effective against different kinds of Gram-negative, Gram-positive, and anaerobic bacteria. Carbapenems fall under class III drug in BCS classification. This classification is based on their high solubility and low permeability. They are used to treat life threatening infections that do not respond to standard antibiotic therapy. They are called “Last line agents”or “Antibiotics of last resort”. The first carbapenem was discovered in 1976.It was initially named Thienamycin and was isolated from Streptomyces cattleya. Derivatives 0f carbapenems are imipenem, panipenem, ertapenem, doripenem, meropenem, biapenem and tebipenem. Carbapenems are available in injectable forms.Oral formulations are challenging because they do not pass easily through the gut wall.

Chemical Structure

Carbapenem has a basic structure of 1, azabicyclo [3.2.0] hept-2-ene2-carboxylic acid. Carbapenems are similar to penicillin. They have a five member ring that isn’t fully saturated and is attached to a beta-lactam ring. In penicillin, carbon replaces the sulfur atom. There is a double bond between C2 and C3.They also have a t-1-hydroxyethyl side chain on the beta-lactam ring. The carbon at position 1 improves stability. The double bond between C2 and C3 is called "Penem” and the carbon at position 1 is known as "Carbo." This is why it is called Carbapenem.



Chemical Name	Chemical Structure
(5*R*,6*S*)-6-[(1*R*)-1-hydroxyethyl]-3-({2-[(iminomethyl)amino]ethyl}thio)-7-oxo-1-azabicyclo[3.2.0]hept-2-ene-2-carboxylic acid IMIPENEM	
(5*R*,6*S*)-3-{[(3*S*)-1-ethanimidoylpyrrolidin-3-yl]sulfanyl}-6-[(*1R*)-1-hydroxyethyl]-7-oxo-1-azabicyclo[3.2.0]hept-2-ene- 2-carboxylic acid PANIPENEM	
3-[5-(dimethylcarbamoyl) pyrrolidin-2-yl] sulfanyl-6- (1-hydroxyethyl)-4-methyl-7-oxo- 1-azabicyclo[3.2.0] hept-2-ene-2-carboxylic acid MEROPENEM	
(4*R*,5*S*,6*S*)-3-[(3*S*,5*S*)-5-[(3-carboxyphenyl)carbamoyl]pyrrolidin-3-yl]sulfanyl-6-(1-hydroxyethyl)-4-methyl-7-oxo-1-azabicyclo[3.2.0]hept-2-ene-2-carboxylic acid ERTAPENEM	
(4*R*,5*S*,6*S*)-6-(1-hydroxyethyl)-4-methyl-7-oxo-3-[(3*S*,5*S*)-5-[(sulfamoylamino)methyl]pyrrolidin-3-yl]sulfanyl-1-azabicyclo[3.2.0]hept-2-ene-2- carboxylic acid DORIPENEM	
(4*R*,5*S*,6*S*)-3-(6,7-dihydro-5*H*-pyrazolo[1,2-a][1,2,4]triazol-8-ium-6-ylsulfanyl)-6-(1-hydroxyethyl)- 4-methyl-7-oxo-1-azabicyclo[3.2.0]hept-2- ene-2-carboxylate BIAPENEM	

Techniques

The steps to overcome the challenges of carbapenem include using drugs and pharmaceutical excipients as transport protein inhibitors, creating prodrug formulations and developing nano carrier based formulations.

Prodrug formulation

The prodrug approach has been widely studied to improve the poor oral bioavailability of carbapenems. Several prodrugs have been created to boost the oral absorption of the main carbapenem compounds. One established method is forming ester prodrugs from β-lactam antibiotics to enhance oral uptake. After these ester prodrugs enter the bloodstream, serum or tissue carboxyesterases break them down and release the active parent drug. Different ester prodrugs of the acidic forms of meropenem (MER) have been developed. They show better bioavailability and maintain the original antibacterial activity profile

Drugs as transport protein inhibitors

To improve the oral bioavailability of meropenem (MER), it may be necessary to block efflux protein transporters such as P-glycoprotein (P-gp). These transporters limit drug absorption. Several compounds, including quinidine, verapamil, and vinblastine, are known P-gp inhibitors. They have been shown to reduce the activity of these transport proteins. Coadministering these inhibitors with P-gp substrate drugs is expected to improve intestinal absorption and systemic exposure of the substrates. This might increase the bioavailability of meropenem.

Pharmaceutical excipients as transport protein inhibitor

Excipients are pharmacologically active ingredients of a dosage form which can influence transport protein functionality; therefore, the use of excipients that inhibits secretory transporters may increase the bioavailability of substrates for each of these proteins. Surfactants such as Cremophor EL, Cremophor RH40, and Polysorbate 80 havshown to increase the bioavailability of efflux transporter substrates due to their inhibitory effects on these proteins.

Similarly, approaches to this have also been using polymers which can inhibit transport proteins such as P-glycoprotein (P-gp), which can increase oral drug bioavailability. The polymers studied include thiolated poly(acrylic acid), thiolated chitosan derivatives (N-octyl-O-sulfate chitosan and chitosan-4-thiobutylamide),poloxamer(Pluronic P85) and Eudragit polymers(Eudragit L100-55,Eudragit S 100 enteric coat/PH dependent)and Eudragit RS100(pH independent/time dependent).

Lipids (phosphatidylcholine (PC), dipalmitoyl PC (used in liposome formulations), may reduce expression of P-gp thus improving absorption of P-gp substrates such as meropenem (MER).

Cyclodextrins such as dimethyl-β-CD, β-CD, and γ-CD have also been studied for their ability to block P-gp activity.

Polyethylene glycol and its derivatives, (PEG 200, 300, and 400), and tocopheryl polyethylene glycol 1000-succinate can also act as P-gp inhibitor. These substances can be used as excipients to enhance the absorption of drugs that are substrates for P-gp.

Nanocarrier-based formulations

There are many different types of nanoparticles or nanosized carriers also known as polymeric and lipid based nanocarriers (eg: solid, lipid nanoparticles, liposomes, inorganic nanocarriers and polymeric miscelles). Different types of nanoparticles have been used as carriers for the delivery of anti-microbial agents in various ways. The application of nanoparticles in drug delivery system can enhance the efficacy, safety and convenience of the therapy.

The drug is absorbed by the body and increase the amount of drug that reaches the bloodstream, whether given by injection or taken by mouth.
NPs have advantages for parenteral drug delivery for several reasons including:

- Poor solubility
- Limited stability
- Fast clearance from the systemic circulation.

For oral delivery, nanocarriers offer several potential advantages, such as:

- Improving physicochemical stability,
- Protection from enzymatic degradation,
- Prolonged residence time in blood,
- Targeting a specific site,
- Improved aqueous solubility and dissolution rate,
- Improved lymphatic transport, and
- Decrease in accessibility by efflux by transporter proteins.

Altogether, these benefits add up to better oral absorption and thus better oral bioavailability and more bioactive compound. Beyond acting delivery vehicles, nanostructured materials may also present antimicrobial properties. Organic and inorganic nanoparticles may potentially serve to mitigate drug-resistant bacteria through competitive inhibition of resistance mechanism or applicable antimicrobial activity.

Indication and adverse effects

Imipenem

Medicinal Uses: Treatment of severe complicated skin, tissue, joint, respiratory tract, intra-abdominal, urinary tract and urogenital infection. Meningitis, endocarditis and sepsis.

ADR: Confusion, convulsion, dizziness, skin rashes, wheezing.

Panipenem

Medicinal Uses: Treatment of listeriol meningitis in pediatrics, respiratory tract infections, urinary tract infections

ADR: Diarrhoea, nausea, vomiting, allergic symptoms such as rash, urticaria

Meropenem

Medicinal Uses: To treat skin and abdominal infections and meningitis, pneumonia

ADR: Seizures, Head ache, confusion, tingling sensation.

Doripenem

Medicinal Uses: Complicated intra-abdominal infections, complicated UTI including pyelonephritis, nosocomial Pneumonia.

ADR: Nausea, vomiting, diarrhea, hypersensitivity reaction like anaphylaxis, rash, utricaria, Stevens Johnson syndrome, anxiety, insomnia

Ertapenem

Medicinal Uses: Community acquired pneumonia, complicated intra abdominal infections, complicated UTI, Pelvic infections

ADR: Diarrhoea, nausea, vomiting, phlebitis, confusion, disorientation, somnolence.

Biapenem

Medicinal Uses: Intra abdominal infections, lower respiratory infections, complicated UTI

ADR: Diarrhea, nausea, itching, rashes, increased white blood cells eosinophils, increased alkaline phosphatase level in blood, increased aspartate aminotransferase, increased alanine aminotransferase. Drugs fever, drug eruption, watery diarrhea.

Tebipenem

Medicinal Uses: Otolaryngologic infection, respiratory infections, otitis media, pneumonia, sinusitis.

ADR: Diarrhea, watery stool, mushy stool, thrombocytosis.

Formulations available

- Powder for IV infusion
- Intravenous infusion
- Injectable solution for IV/ IM
- Powder for solution
- Orally bioavailable(not approved)
- Dry powder inhaler

Dry powder inhaler formulation

Micronization helped achieve the desired particle size range of 1-5 μm .The particle size of the meropenem (MPN) were characterized using scanning electron microscopy (SEM) and transmission electron microscopy (TEM) techniques. Every different batches of formulations, (each with a total weight of 2.0 g), was stored in the refrigerator at 4–8 °C (pure drug, micronized drug and filled capsules) and a measure of how uniform the drug was mixed throughout the powder was done by calculating the average drug content and variability between samples. Every formulation applied had 10 doses of drug (25 mg of drug in 100 ml of HPLC grade water). The content of the drug was measured by an official HPLC method validated by the laboratory. The test for homogeneity gave a result where the content of drug was100 % ± 5 % (Mean ± S.D.) And drug content was quantified using a validated high-performance liquid chromatography (HPLC) assay. The homogeneity test showed a mean drug content of 100 % ± 5 % (Mean ±S.D) with a coefficient of variation less than 5% for samples (Crooks and Ho, 1976).

Powder for injections

Meropenem breaks down a lot when samples are reconstituted and left in a saline solution. The drug lost nearly 80% of its effectiveness after 36 hours of exposure to 45°C.When subjected to chromatographic analysis three distinct degradation peak appeared at three different time points: 3.0 mins, 17.0 mins during detection at 220nm.The powder form of meropenem demonstrate superior heat stability when dry heat is applied compared to its other

formulation. The medication maintained its complete stability during the testing periods at 70°C.The compound experienced minimal degradation because only 8% of its total amount decompost after 115 days. At 90°C about 75%of the drug broke down after 95 days, but there were no significant break down peaks detected. Chromatographic analysis showed only a small peak at 0.3 mins under 220 nm detection. Meropenem stays much more stable in its solid form when exposed to dry heat compared to when its dissolved in a solution. This is because the drug breaks down quickly in solution when temperature are high.

Unavailable formulations

- Tablet
- Capsule
- Suspension
- Emulsion
- Cream
- Paste
- Gel

Available marketed products

- Doripenem for injection
- Doripenem for injection 500mg
- Meropenem injection I.P(500/1000MG)
- Imipenem and Cilastatin injection I.P 500mg

Conclusion

Carbapenems are a important class of β-lactam antibiotics due to their activity against diverse bacterial species and stability to a number of hydrolytic enzymes that degrade other antibiotics. But their use in the medicine can be limited because they don't dissolve well in the water. Their clinical effectiveness can be limited by poor aqueous solubility, leading to challenges in formulation development, bioavailability, and therapeutic efficacy. This review highlights various strategies employed to enhance the solubility profile of carbapenems, including salt formation, pH adjustment, co-solvent systems, solid dispersions, complexation with cyclodextrins, nanoparticle technology, and lipid based formulations.

Improving the solubility of carbapenems is crucial for optimizing their pharmacokinetic profiles, enhancing therapeutic efficacy, and expanding their clinical applications. A multidisciplinary approach involving pharmaceutical sciences, nanotechnology, and regulatory insights will be essential to drive the development of next-generation carbapenem formulations with improved solubility and clinical outcomes.

References

1. Raza A, *et al*. Oral Meropenem for Superbugs: Challenges and Opportunities, Drug Discovery Today, 2020, 00.
2. Coulthurst SJ, *et al*. Regulation and Biosynthesis of Carbapenem Antibiotic in Bacteria, Nature Reviews Microbiology, 2005, 3.
3. Potter RF, *et al*. The Rapid Spread of Carbapenem-Resistant Enterobacteriaceae, Drug Resistance Updates, 2016, 29.
4. Cielecka-Piontek J, *et al*. Comparative Review of Analytical Techniques for Determination of Carbapenem, Current Analytical Chemistry,2012:8:91–115.
5. EL-Gamel MIE, *et al*. Recent updates of carbapenem antibiotics, European Journal of Medicinal Chemistry,2017:131:185–195.
6. Cielecka-Piontek J, *et al*. Recent Updates In Stability Studies Of Matthew Carbapenems, Current Pharmaceutical Analysis,2011:7:213–227.
7. Lamb A, *et al*. Approaches to enhance the anti microbial activity of carbapenems within bacterial biofilms, RSC Pharmaceutics,2024:1(4).
8. Goa KL, *et al*. Panipenem/betapenem, Drugs, 2003.
9. Matthews SJ, Doripenem monohydrate, a broad-spectrum carbapenem antibiotic, Clinical Therapeutics,2009:31(1).
10. Scholar E, Ertapenem, xpharm: The comprehensive pharmacology reference, 2007.
11. Vora A, *et al*. Biapenem, Journal of the Association of Physicians of India, 2022.
12. Mahalingam A, Tebipenem, A novel oral carbapenem.
13. Muneer S, Development and characterization of meropenem dry powder inhaler formulation for pulmonary drug delivery, International Journal of Pharmaceutics, 2020, 587.
14. Mendez ASL, *et al*. Stability and degradation kinetics of meropenem in powder form injection and reconstituted sample, Journal of Pharmaceutical and Biomedical Analysis, 2006, 41.