Review Article **ISSN: 2349 – 4492**

Asian Journal of Research in Biological and Pharmaceutical Sciences

Journal home page: www.ajrbps.com

https://doi.org/10.36673/AJRBPS.2022.v10.i03.A11

ANALYTICAL AND BIOANALYTICAL METHODS FOR ESTIMATION OF MEROPENEM ALONE AND IN COMBINED DOSAGE FORMS AN OVERVIEW

Diptimayee Jena[*1], Snigdha Rani Behera[1], Gowri Sankar Chintapalli[1], Kailash Nath Das[1], Priyam Joshi[1], Kirtimaya Mishra[1]

[1*]School of Pharmacy, ARKA JAIN University, Jamshedpur, Jharkhand, India.

ABSTRACT

This review work is a compilation of previously published methods for analysing Meropenem, either alone or in combination with other drugs. Many spectroscopic methods, such as derivative techniques and chromogenic techniques, were employed. A new and improved chromatographic method based on biological fluids and pharmaceutical formulations is also available. Aside from these two techniques, there are a few LC-MS/MS and HPTLC methods. In today's analytical research world, the quality by design or design by expert technique is used to obtain a better method for method validation. This concise review work can help an analyst choose the best method for developing and validating analytical methods.

KEYWORDS

Meropenem, Analysis, Analytical method development, HPLC and UV.

Author for Correspondence:

Diptimayee Jena,

School of Pharmacy,

Arka Jain University,

Jamshedpur, Jharkhand, India.

Email: diptijena72@gmail.com

INTRODUCTON

A revolution in human health has been discovered as pharmaceuticals advance daily. Pharmaceuticals that are pure and free of impurities will function at their peak. Various chemical and instrumental techniques were developed to make drugs free of impurities on a regular basis. Impurities can appear at any point in the production process, from the manufacturing of bulk drugs to the packaging of finished goods, and even during storage (degradation). Impurities may frequently appear during the two phases of storage and transportation. Impurities must therefore be found and measured in these conditions. Instrumentation and methods for analysis play a significant role in detection and quantification[1].

Intermediate pharmaceutical analysis, which covers a variety of stages including testing of bulk drugs, intermediate products, drug formulations, degradation products, chemical stability of drugs, and toxic contents of a drug materials, becomes a crucial tool for therapeutic process monitoring. Today, polypharmacy is a highly beneficial treatment for many diabetic patients. Therefore, quality control testing of combined formulations and assay of biological samples are crucial for improving polypharmacy therapy.

Drugs called antibiotics are prescribed to treat bacterial infections in both humans and animals. They either eradicate bacteria or make it difficult for them to proliferate and spread[2].

Members of the beta lactam class of antibiotics, such as penicillins and cephalosporins, carbapenems kill bacteria by attaching to penicillin-binding proteins and preventing the synthesis of bacterial cell walls[3]. The majority of the time, complex bacterial infections are treated with carbapenems because of their distinctive pharmacological characteristics. When treating patients empirically for severe nosocomial infections of unknown origin, a carbapenem is frequently combined with an antibiotic that targets Gram-positive bacteria[4]. In 2012, the drugs imipenem-cilastatin, meropenem, ertapenem, doripenem, panipenem-betamipron, and biapenem were removed from the black triangle list due to short-term clinical trials showing no increased risk of acute pancreatitis[5]. Imepenem-cilastatin, meropenem, ertapenem, doripenem, panipenem-betamipron, and biapenem are examples of medications in the carbapenem class. Table No.1 provides information about the drugs in the carbapenem class.

Meropenem

In this journal, Meropenem is briefly discussed among all of these carbapenem class medications.

Chemically, meropenem (4R,5S,6S) ((3S,5S)-5-(Dimethylcarbamoyl) pyrrolidin-3-yl)thio) (R)-1-hydroxyethyl) -6 -4-methyl -7-oxo-1-azabicyclo [3.2.0] Acid hept-2-ene-2-carboxylic (Figure No.1) is Meningitis (infection of the membranes surrounding the brain and spinal cord) and skin and abdominal (stomach area) infections brought on by bacteria are treated in adults and children 3 months of age and older with meropenem injections. Meropenem injection belongs to the category of drugs known as antibiotics. It functions by eradicating the infection-causing bacteria. Colds, the flu and other viral infections cannot be treated with antibiotics like meropenem injection. Antibiotic use that is not necessary increases the likelihood of developing a later infection that is resistant toantibiotic treatment.

There have been several reports of analytical techniques based on UV, RP-HPLC and LC-MS/MS for determining the pharmacokinetics of meropenem phosphate in plasma and urine of people, rats, and dogs.

The analytical techniques available for the estimation of Meropenem, including electrochemical methods, UV/VIS spectrophotometric methods, HPLC/LC-MS, GC-MS, and CE/CE-MS, are the focus of this review article. Table No.2 and Table No.3 discuss the specifics of the prior studies.

Quality by Design

For pharmaceuticals, several analytical methods are available to enhance the quality[26-31]. But currently, the Quality by Design technique is widely used to improve the analytical method. For the development and production of pharmaceuticals, quality by design (QbD), which is covered in ICH Q8[1], Q9, and Q2, is well-established[32].

Benefits of Quality by Design Method

It supports the growth of a reliable methodology. Variability sources can be better controlled according to the design setup. Method When a method is transferred from the quality control department to the research level, the success of the transfer is higher. Through ongoing improvement throughout the lifecycle, this technique creates a space for the development of new techniques[33].

Table No.1: Details of carbapenem class drugs

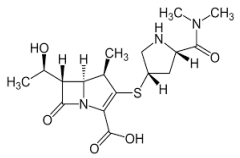
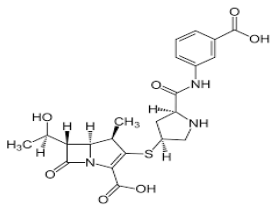
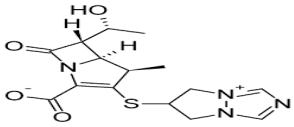
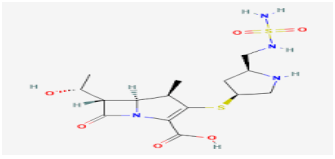
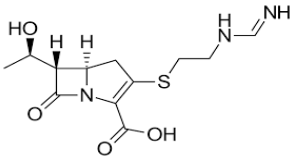
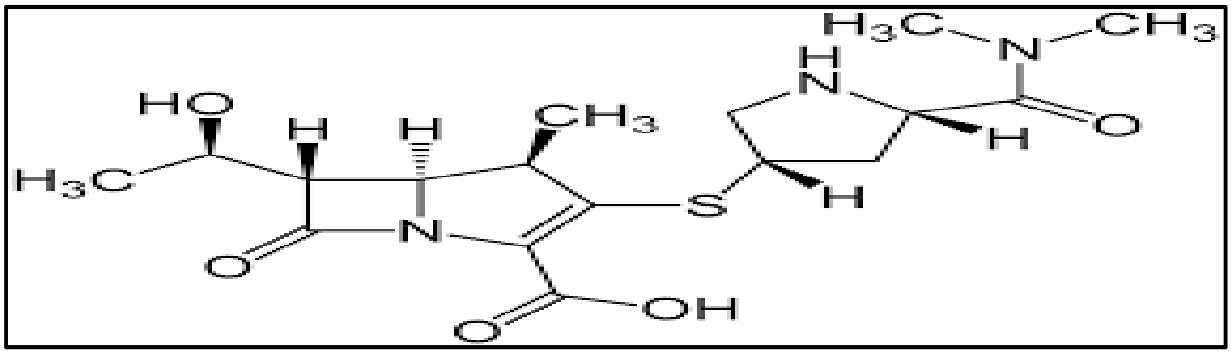
S.No	Drugs	Structure	IUPAC name	Molecular weight	Solubility
1	Meropenem		4R, 5S, 6S)-3-(((3S, 5S)-5-(Dimethylcarbamoyl) pyrrolidin-3-yl)thio)-6-((R)-1-hydroxyethyl)-4-methyl-7-oxo-1-azabicyclo [3.2.0] hept-2-ene-2-carboxylic acid	383.464g/mol	Soluble in water (8mg/ml at 25°C), 5% monobasic potassium phosphate solution, ethanol (<1mg/ml at 25°C) and DMSO (77mg/ml at 25°C).
2	Ertapenem		Sodium; 3-[[(2*S*, 4*S*)-4-[[(4*R*, 5*S*, 6*S*)-2-carboxy-6-[(1*R*)-1-hydroxyethyl]-4-methyl-7-oxo-1-azabicyclo[3.2.0] hept-2-en-3-yl] sulfanyl] pyrrolidine-2-carbonyl]amino] benzoate	475.516g/mol	Soluble in water and slightly soluble in methanol
3	Biapenem		(4R, 5S, 6S)-3-(6, 7-dihydro-5H- 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	350.39g/mol	Soluble in water (≥5mg/ml, warmed), DMSO (<1mg/ml at 25°C), and ethanol (<1mg/ml at 25°C).
4	Doripenem		(4R, 5S, 6S)-6-(1-Hydroxyethyl)-4-methyl-7-oxo-3-(((5S)-5-((sulfamoylamino) methyl) pyrrolidin-3-yl) thio)-1-azabicyclo [3.2.0] hept-2-ene-2-carboxylic acid	420.5043g/mol	Sparingly soluble in water, slightly soluble in methanol, and practically insoluble in ethanol
5	Imipenem		(5R, 6S)-6-[(1R)-1-hydroxyethyl]-3-({2-[(iminomethyl) amino] ethyl}thio)-7-oxo-1-azabicyclo [3.2.0] hept-2-ene-2-carboxylic acid	299.347g/mol	Soluble in water and slightly soluble in methanol

Table No.2: Details about HPLC analytical method development

S.No	Stationary phase(column)	Mobile phase	Ph	Wavelength	Flow rate	Reference
Meropenem and Vaborbactam						
1	Column Kromasil 250 x 4.6mm, 5m	Buffer and acetonitrile in the ratio of 50: 50% v/v		250nm	1ml/min	6
2	Column xterrac8 150x4.6mm, 5µm.	Water: acetonitrile: methanol (20:30:50% v/v)		297nm	1ml/min	7
3	C18 (250mm x 4.6mm x 2.6µm)	Buffer : Methanol (70: 30%v/v)	6	242nm.	1ml/min	8
4	C8 Column (25cm × 4.6mm, 5µm	Methanol and potassium dihydrogen phosphate (0.1 Molar) mixed in ratio 65/35 (v/v).		235nm	six min	9
5	Aquity UPLC, Hibar C18 (100mm×2.1mm, 2µm)	Acetonitrile and 0.01N Potassium dihydrogen ortho phosphate (KH2PO4) (50:50% v/v)	3	250nm	0.3ml/min	10
6	C-18 Column	0.03M di-hydrogen phosphate buffer and acetonitrile at a ratio of 80:20,	3	298nm	1mL/min	11
7	C-18(4.6mmx 250mm) 5µ	Water ,acetonitrile and methanol in specific composition		300nm	1.5ml/min	12
Biapenem						
8	(4.6mm x 150mm) Column	acetonitrile -0.1 mol/l sodium acetate (2:98, v:v)	4	300nm	1.0ml/min	13
Doripenem						
9		methanol and phosphate buffer		295nm	1.5ml/min	14
10	C18 Column (250 × 4.6mm, 5µm)	acetonitrile and ammonium acetate (0.012M aqueous solution 15:85.%V/V	6.73	295nm	0.5ml/min	15
Ertapenem						
11	RP.18, 5µm particle size, 250 × 4mm I.D.	. phosphate buffer 25mmol L.1 and methanol (85:15 v/v)	6.5	294nm	1.2mL min.1	16
Meropenem and Amoxyclilin						
12	Cromosil C18 Column (250 mm × 4.6 mm i.d, 5m)	phosphate buffer and acetonitrilein the ratio of 70: 30 v/v	6.8	229nm	1.0ml/min	17
13	Column (Metachem† LC RP-18, with 250mm_/4.6mm i.d. and 5mm	30mM monobasic phosphate buffer and acetonitrile (90:10; v/v),	3	298nm.	1.0ml/min	18

Table No.3: Details about Spectroscopic method development

S.No	Drug	Method	Description	Reference
1	Stability-indicating derivative spectrophotometry method for the determination of biapenem in the presence of its degradation products.	Spectroscopic method	Detection wavelength: 278nm and 312nm Linearity range: (1.60-9.60) × 10-2 Correlation coefficient – r: 0.9993 for278nm and 0.9941 for 312nm respectively. %RSD: intra-day repeatability (RSD from 0.41% to 2.16%) and inter-day repeatability (RSD 0.64% and 0.96%)	19
2	Sodium in primaxin by the first order derivative ultraviolet spectrophotometric determination of imipenem and cilastatin	UV-Spectrometric Method	Detection wavelength: 306 and 312nm Linearity range: 14-42mg ml-1 Correlation coefficient: (r = 0.9998 %RSD:IMIPENEM-UV: 1.9%, LC:2.3%LC/UV=2.3%* Cilastatin -UV :1.7 LC:1.7 UV/LC=1.8	20
3	Utraviolet spectrophotometry [dual wavelength and cheometric] and high performance liquid chromatography for simultaneous estimation of meropenem and salbactum sodium in pharmaceutical.	UV= spectrophotometric method.	Detection wavelength: 242nm and 274nm for determination of MERM, 285nm and 306nm for determination of SB Linearity range: MERM and SB were linear in the range of 4–24µg/mL and 2–12µg/mL, respectively. Correlation coefficient -r:PLS 0.996 and SB 0.997 PCR MERM 0.997 and SB 0996 %RSD: Intraday and interday<2	21
4	Solid-state stability study of meropenem solution based on spectrometric analyis	Spectrophotometric method.	Detection wavelength: zero crossing wavelength of 307nm and first derivative spectroscopy ny= (111, 30 ±2, 27) × (λ = 320nm). Linearity range: range 25-131µg/mL %RDS: Inter-day repeatability also had acceptable values 99.9% to 101.3%	22
5	Spectrophotometric Method for the Estimation of Meropenem in Pure and in Market Formulation Meropenem	Spectroscopic method	Detection wavelength: 477nm Linearity range: e 15-70µg/mL correlation coefficient	23
6	Development and Validation of UV Spectrophotometric and RP-HPLC Methods for Determination of Ertapenem During Stability Studies	Spectroscopic method	Detection wavelength = 294nm.	24
7	Spectroscopic method of estimation of meropenem and salbatumsodium in combined dosages from by frist order derivative method.	Spectroscopic method	Detection wavelength = 333nm and 252nm Linearity range = 5-70µg/ml	25



(4R, 5S, 6S)-3-(((3S, 5S)-5-(Dimethylcarbamoyl) pyrrolidin-3-yl) thio)-6-((R)-1-hydroxyethyl)-4-methyl-7-oxo-1-azabicyclo [3.2.0] hept-2-ene-2-carboxylic acid

Figure No.1: Chemical structure and IUPAC name of Meropenem

CONCLUSION

This study presents developed and verified chromatographic and spectrophotometric techniques for the evaluation of Meropenem. The different spectroscopic and chromatographic methods for Meropenem are available for both the individual component and the combination, according to this review. It has also been determined that the majority of the chromatographic methods have more resolution thanks to a mobile phase made up of phosphate buffer, methanol and acetonitrile. It was found that the most popular form of meropenem used was (ex. MERREM). For chromatographic methods, flow rates between 0.8 and 1.5ml/min have been found to produce good retention times. The most common solvent for most spectroscopic techniques is methanol. As a result, all of the methods were discovered to be straightforward, accurate, affordable, precise, and repeatable. However, it is evident from this review that the use of the Design of Expert (DOE) technique can enhance the currently used methods and produce results that are more accurate and precise.

ACKNOWLEDGMENT

The School of Pharmacy at ARKA JAIN University in Jamshedpur, Jharkhand is acknowledged by the authors for its consistent support throughout the project.

CONFLICT OF INTEREST

The authors affirm that they do not have any competing interests.

BIBLIOGRAPHY

1. Siddiqui M R, AlOthman Z A, Nafisur Rahman. Analytical techniques in pharmaceutical analysis: A review, *Arabian Journal of Chemistry,* 10(1), 2017, 1409-1421.
2. Matthew, Hutchings A, Truman W, Barrie W. Antibiotics: Past, present and future, *Current Opinion in Microbiology,* 51, 2019, 72-80.
3. Biljana A, Jill B, Ana C, Milan M, Nevena S, Predrag N. 16-membered macrolide antibiotics: A review, *Int J Antimicrob Agents,* 51(3), 2018, 283-298.
4. Palanisamy P, Gowdhaman K, Jaykar B, Margret C R, Venkateswarlu B S, Pasupathi A. Formulation and evaluation of film coated tablets of azithromycin USP, *International Journal of Medicine and Pharmacy,* 1(1), 2013, 59-70.
5. Tilman C S, Liege, Belgium. Gliptins, dipeptidyl peptidase-4 inhibitors, and risk of acute pancreatitis, *Pubmed,* 12(4), 2013, 545-557.
6. Balaswami B, Ramana P V, Rao B S, Sanjeeva P. A new simple RP-HPLC method for simultaneous estimation of Meropenem and Vaborbactamin tablet dosage form, *Asian. J. Research Chem,* 11(1), 2018, 111-116.
7. Vani R, Naheed S K S. Analytical method development and validation of Meropenam and Vaborbactam by RP-HPLC, *International Journal of Pharmacy and Analytical Research,* 10(2), 2021, 146-153.

8. Mounika K, Reddy L R, Dhachinamoorthi D. Analytivcal method development validation of Meropenem and Vaborbactam of pure and dosage forms using RP-HPLC method, *World Journal of Pharmaceutical and Life Sciences,* 5(9), 2019, 150-160.
9. Sreeja V, Kumari R V V, Kumar M S, Marakatham S. Development and validation of an RP-HPLC method for simultaneous estimation of Meropenem and Vaborbactam in bulk and dosage form, *JETIR1907A13 Journal of Emerging Technologies and Innovative Research (JETIR),* 6(6), 2019, 934-942.
10. Masthanamma S K, Firdous M D H, Monika D N V, Chinababu D. Stability indicating RP-UPLC method development and validation for the simultaneous determination of meropenem and varobactum in bulk and their combined dosage form, *Int. J. Pharm. Sci. Rev. Res,* 59(1), 2019, 88-94.
11. Khanum R, Mallikarjun C, Qureshi M, Mahandas K, Rathore M J. Development and validation of a RP-HPLC method for the detection of Meropenem as a pure compound in a pharmaceutical dosage form and post thermal induced degradation, *International Journal of Pharmacy and Pharmaceutical Sciences,* 6(4), 2014, 149-152.
12. Negi V, Chander V, Singh R, Sharma B, Singh P, Upadhaya K. Method development and validation of Meropenem in pharmaceutical dosage form by RP-HPLC, *Indian Journal of Chemical Technology,* 24(4), 2017, 441-446.
13. Zhao L, Liu Y, Kou Z, Bayasi A, Cai H, Zhang C, Wang Q, Li Y, Fang Y. Improved RP-HPLC method to determine Biapenem in human plasma/urine and its application to a pharmacokinetic study, *Arzneimittelforchung,* 61(3), 2011, 197-204.
14. Sutherland C, Niolau D P. Development of an HPLC method for the determination of Doripenem in human and mouse serum, *Journal of Chromatography B,* 853(1-2), 2007, 123-126.
15. Kurien J, Jayesekhar P. Stability indicating HPLC determination of Doripenem in pharmaceutical dosage forms, *Int. J. Pharm. Sci. Rev. Re,* 22(2), 2013, 41-45.
16. Zajac M, Piontek JC,Jelinska A. Development and validation of UV Spectrophotometric and RP-HPLC methods for determination of Ertapenem during stability studies, *Chem. Anal. (Warsaw),* 51, 2006, 761-770.
17. Deshmuk N, Patel R, Das P K. Development of quantitative method for analysis of meropenem and amoxycillin by RP-HPLC method, *Pharmaceutical and Biological Evaluations,* 3(4), 2016, 431-436.
18. Mendez A S L, Steppe M, Schapoval E E S. Validation of HPLC and UV Spectrophotometric methods for the determination of Meropenem in pharmaceutical dosage form, *Journal of Pharmaceutical and Biomedical Analysis,* 33(5), 2003, 947-954.
19. Piontek J C, Lunzer A. Stability indicating derivative spectrophotometry method for the determination of Biapenem in the presence of its degradation products, *Central European Journal of Chemistry,* 9(1), 2011, 35-40.
20. Forsyth R J, Ip D P. Determination of imipenem and cilastine sodium in primaxin® by first order derivative ultraviolet spectrophotometry, *Journal of Pharmaceutical and Biomedical Analysis,* 12(10), 1994, 1243-1248.
21. Marwada K R, Patel J B, Patel A J. Ultraviolet spectrophotometry (dual wavelength and chemometric) and high performanceliquid chromatography for simultaneous estimation of Meropenem and Sulbactam sodium in pharmaceutical dosage form, *Spectrochimica Acta Part A: Molecular and Biomolecular Spectroscopy,* 124, 2014, 292-299.
22. Piontek J C, Paczkowska M, Lewandowska K, Barszcz B. Solid-state stability study of Meropenem-solutions based on spectrophotometric analysis, *Chemistry Central Journal,* 7(98), 2013, 1-9.
23. Qassim A W. Spectrophotometric method for the estimation of meropenem in pure and in market formulation meropenem, *Chemistry and Materials Research,* 7(4), 2015, 59-66.

24. Ali S M, Bharath P, Sharif S K, Ramachandran D. Simple and fast stability indicating UPLC method for the simultaneous quantification of Meropenem and remogliflozin Etabonate in bulk drug and formulations, *Current trends in Biotechnology and Pharmacy,* 15(4), 2021, 401-407.
25. Shaikh N K, Jat R, Bhangale J O. Analysis of meropenem and nateglinide for simultaneous estimation using spectro-chromatographic methods, *European Journal of Molecular and Clinical Medicine,* 7(8), 2020, 741-755.
26. Amani B, Babu G R, Mulukuri N V L S. A novel spectroscopic method for the simultaneous determination of pregabilin and meropenem in synthetic mixture, *Int. Res. J. Pharma,* 8(10), 2017, 153-156.
27. Mishra K, Saragi B, Burala K K. Simultaneous estimation of sertraline and alprazolam in its bulk and tablet dosage form by RP-HPLC method, *Asian Pacific Journal of Pharmacy and Phytochemistry,* 1(1), 2016, 25-32.
28. Mishra K, Prasanna K D, Behera S R. Simultaneous estimation of sacubitril and valsartan in bulk and pharmaceutical dosage form by using RPHPLC, *Research Journal of Pharmacy and Life Sciences,* 1(2), 2020, 25-32.
29. Balamurugan K, Mishra K, Suresh R. Simultaneous estimation of linagliptin and metformin hcl in human plasma by RP-HPLC method, *International Research Journal of Pharmacy,* 10(1), 2019, 01-04.
30. Mishra K, Behera S R, Mishra S R, Somesu M, Kumar B K. A validated stability indicating rp-hplc method development for platelet aggregation inhibitor ticagrelor in bulk and tablet formulation, *Journal of Global Pharma Technology,* 11(12), 2019, 12-18.
31. Mishra K, Kumar B K, Kumari M M, Subrahmanyam B S S. New analytical method development and validation of chlorpheniramine maleate by using UV-visible spectrophotometry, *Indo American Journal of Pharmaceutical Sciences,* 3(7), 2016, 767-772.
32. Mishra K, Behera S R, Sankar C G, Martha S K. Development and validation of stability indicating assay method (SIAM) for rabeprazole in rabeprazole sodium delayed release tablets using HPLC, *Research Journal of Pharmacy and Life Sciences,* 1(3), 2020, 89-97.
33. Sun L, Zhang W, Liu X, Sun J. Preparation and evaluation of sustained-release azithromycin tablets *in vitro* and *in vivo*, *Asian Journal of Pharmaceutical Sciences,* 9(3), 2014, 155-161.

Please cite this article in press as: Diptimayee Jena *et al*. Analytical and bioanalytical methods for estimation of meropenem alone and in combined dosage forms an overview, *Asian Journal of Research in Biological and Pharmaceutical Sciences,* 10(3), 2022, 116-123.