REVIEW PAPER

METHODS FOR DETERMINATION OF MEROPENEM CONCENTRATION IN BIOLOGICAL SAMPLES

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Received: 08.11.2021.
Accepted: 26.01.2022.

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DOI: 10.2478/sjecr-2022-0005

ABSTRACT

Measuring the concentration of antibiotics in biological samples allow implementation of therapeutic monitoring of these drugs and contribute to the adjustment of the dosing regimen in patients. This increases the effectiveness of antimicrobial therapy, reduces the toxicity of these drugs and prevents the development of bacterial resistance. This review article summarizes current knowledge on methods for determining concentration of meropenem, an antibiotic drug from the group of carbapenems, in different biological samples. It provides a brief discussion of the chemical structure, physicochemical and pharmacokinetic properties of meropenem, different sample preparation techniques, use of apparatus and equipment, knowledge of the advantages and limitations of available methods, as well as directions in which new methods should be developed. This review should facilitate clinical laboratories to select and apply one of the established methods for measuring of meropenem, as well as to provide them with the necessary knowledge to develop new methods for quantification of meropenem in biological samples according to their needs.

Keywords*: meropenem, methods for determination, chromatographic methods, biological samples, therapeutic drug monitoring*

INTRODUCTION

Measuring the concentration of antibiotics in biological samples (e.g. plasma, serum) would allow for therapeutic drugs monitoring (TDM) of antibiotics in patients and determination of their pharmacokinetic (PK) and pharmacodynamic (PD) properties in order to achieve the appropriate PK/PD targets. Also, it would contribute the dosage regimen to be adjusted in order to increase the effectiveness of the therapy, while at the same time reducing the possibility of overdose and microbial resistance.

The total global antibiotic consumption expressed in defined daily doses (DDD) for period from 2000 to 2015 years are increased 65%, and in the 2015 year was 34.8 billion DDDs. During this period was the rapid increase in the use of last-resort compounds such as glycylcyclines, oxazolidinones, carbapenems, and polymyxins, which is of particular concern (1). Carbapenems (e.g. meropenem) are class of major family of β-lactams antibiotics, to which it also belongs a class of penicillins (e.g. piperacillin) and a class of cephalosporins (e.g. ceftazidime) (2). β-lactam antibiotics are the most frequently prescribed antimicrobial agents for the treatment of bacterial infections and severe infections in the critically ill. These are time-dependent antibiotics that are effective while their unbound concentrations are above the minimum inhibitory concentration (MIC) of targeted pathogen (%T>MIC) (3, 4). The maximal bactericidal effect of β-lactam is reached when %T>MIC exceeds 40%, 50% and 60–70% of the dose interval for carbapenems, penicillins and cephalosporins, respectively (5-8). On the example of two representatives of cephalosporines- cefepime and ceftazidime, it has been shown that in patients with serious bacterial infections the %T>MIC of 100% displayed significantly greater clinical and bacteriological outcomes (9). In addition to time-dependent antibiotics, there are also concentration-dependent antibiotics, such as fluoroquinolones and aminoglycosides, which achieve high concentrations at the binding site which eradicates the microorganism (10). While time-dependent antibiotics achieve the optimal therapeutic effect when the time that the drug remains above the MIC is equal or greater than 50% of the dosing interval (11), concentration-dependent antibiotics have the strongest antibiotic effect when the concentrations are > 10 times above the MIC for their target organism at the site of infection (10).

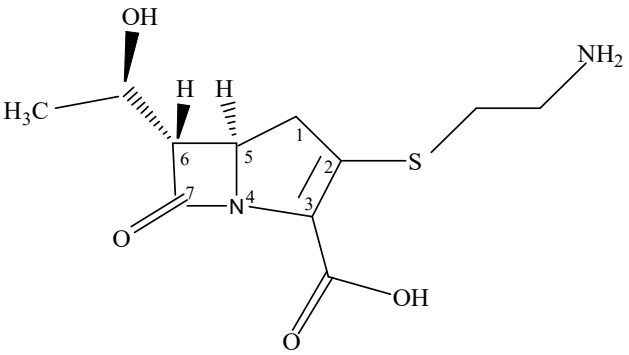
Meropenem, similar to other β-lactam antibiotics, penetrates the bacterial cell wall and inhibits cell wall synthesis, and is an effective treatment for a wide range of infections caused by many aerobic / anaerobic gram-positive and gram-negative organisms (12). Its antibacterial activity is related to the duration of the maintenance of its free concentration above the minimal inhibitory concentration (MIC) during each dosing interval (13). For optimal bactericidal activity of meropenem, the % T>MIC should be about 40%, while for the treatment of severe infections it can be 80% and 100% (14, 15), similarly to cefepime and ceftazidime (9). In cases where clinicians know the MIC of the pathogen that causes infection and plasma concentrations of antibiotics, the effectiveness of therapy is significantly increased, drug-related toxicity is reduced, and bacterial resistance is prevented (16). This is particularly significant in the treatment of critically ill patients, where the concentration of antibiotics are variable and is very difficult to predict due to a wide range of pathophysiological changes (17). Therefore, it is necessary to constantly determine the level of antibiotics in biological samples, within the TDM. On the other side, determination of antibiotics in biological samples demand a highly specific and rapid method as many antibiotics (e.g. β-lactams) have serious stability problems.

The aim of this article is to review the literature and gather information on different methods of measuring the concentration of meropenem in biological samples, both in terms of different techniques of sample preparation and the use of apparatus and equipment. In this way, they will enable clinical laboratories to select and apply one of the developed methods or to develop a new method in accordance with their needs.

MEROPENEM - CHEMICAL STRUCTURE, PHYSIOCHEMICAL AND PHARMACOKINETIC PROPERTIES

Thienamycin is the first member of the carbapenem class within β-lactams antibiotics, was initially isolated from the micro-organism Streptomyces cattleya (Fig. 1). About its properties (antibacterial spectrum and potency) was the first reported by *Kropp et al.* (18), while the structure of thienamycin determined by *Albers-Schonberg et al.* (19). Also, on the physical and chemical properties of thienamycin, as well as the chromatographic procedures of its isolation, was reported *Kahan et. al.* (20). Thienamycin will further serve as the basis for the synthesis of new carbapenems, which represent its derivatives.

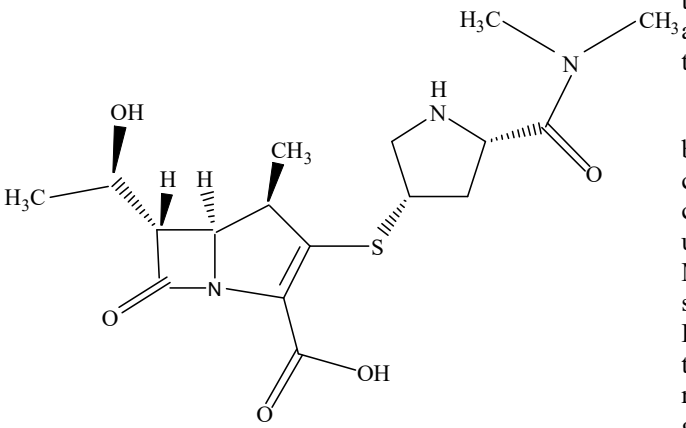
Figure 1. The chemical structure of thienamycin



The basic structure of carbapenem contains a bicyclic ring composed of the 4:5 fused ring lactam of penicillins, with a substitution of carbon for sulfur at C-1 and the presence of double bond between C-2 and C-3, which is a difference compared to penicillins (Fig. 1). A special difference is the presence of hydroxyethyl side chain in the *trans*-configuration at C-6 position compared to conventional penicillins and cephalosporins, which have an acylamino substituent in

the *cis*-configuration at C-6 position on the β-lactam ring. And it is precisely the *trans*-configuration of this side chain that is responsible for the resistance of carbapenems to hydrolysis by β-lactamases (21). Also, the *trans*-configuration of two hydrogen atoms at the C-5 and C-6 positions of the β-lactam ring results in stability against β-lactamases and the hydroxyethyl side chain with *R* configuration has much improved antibacterial potency (22). In addition, the physiochemical properties of carbapenems depend on two other side chains on the bicyclic ring. The side chain at position C-1 is a methyl group that has substituted a hydrogen atom (e.g. meropenem, Fig. 2). The presence of a methyl group at C-l results in much more stability towards hydrolysis by the enzyme dehydropeptidase-I (DHP-1), which is found in the brush border of renal tubular cells and is responsible for rapid hydrolysis of the earlier carbapenems (23, 24). The side chain at position C-2 (a basic alkylthio group) is variable among the carbapenems and to be responsible for the enhanced activity of this compounds (e.g. thienamycin, imipenem, meropenem) against *Pseudomonas aeruginosa* and other gram-negative bacteria (25, 26).

Figure 2. The chemical structure of meropenem



Meropenem was developed in the 1980s, it has come into clinical use in 1996, when it was approved by the *Food Drug Administration* (27, 28). Meropenem, (4R,5S,6S)-3-{[(3S,5S)-5-(Dimethylcarbamoyl)-3-pyrrolidin-3-yl]sulfanyl}-6-[(1R)-1-hydroxyethyl]-4-methyl-7-oxo-1-azabicyclo[3.2.0]hept-2-ene-2-carboxylic acid (Fig. 2), is a β-lactam antibiotics broad spectrum and belongs to the class of the carbapenems. Its structure is similar to imipenem in having a 6-α-hydroxyethyl group at C-6, but differs in having a methyl group attached at C-1 and a dimethylcarbamoylpyrrolidinethio side chain attached at C-2. The presence of a methyl group at C-l provides meropenem with excellent stability to human renal DHP-1, while unique side chain at C-2 assures a broad spectrum of activity which includes *Pseudomonas aeruginosa* and other aerobic and anaerobic organisms (21).

Meropenem is a white to pale yellow crystalline powder with acidic properties, where the pKa1 values of the carboxyl group and the pKa2 values of the secondary amino group in the pyrrolidine ring are 2.9 and 7.4, respectively. The β-lactam ring of meropenem similar to other β-lactam antibiotics is hydrolysed in aqueous solution and this hydrolysis is catalysed by acidic or basic conditions, leading to an antimicrobial inactive compound (12, 29). It is readily soluble in dimethylformamide, dimethylsulfoxide, 5% potassium dihydrogen phosphate and physiological saline solution, very slightly soluble in ethanol and not soluble in acetone and ether (30). As a hydrophilic compound with a low protein binding (2% (31), 7% (32) and 9% (33)), low volume of distribution (~21L) indicating predominantly extracellular distribution and it is partially distributed in the cerebrospinal fluid. The elimination half-life is ~1 hour, and it is mainly eliminated via the kidneys (30, 34).

METHODS OF QUANTIFYING ANTIBIOTICS IN BIOLOGICAL SAMPLES

The agar diffusion method is a microbiological assay (MBA) that is the most widely used for the determination of antimicrobial drugs in biological samples (35). This method has been used to determination of antimicrobial drugs since the 1940s (36-38), after which many reported the use of the agar diffusion method (39-49), as well as modifications of this method (50-53) for the determination of antibiotics.

Various methods for quantification of antibiotics have been reported, the most common being in the last 40 years is chromatographic methods, like high-performance liquid chromatography with ultraviolet detection (HPLC-UV), liquid chromatography with tandem mass spectrometry (LC-MS) and more recently liquid chromatography with two mass spectrometry detectors (LC-MS/MS). The application of the HPLC methods for the measurement of antibiotic concentrations in biological samples in clinical microbiology laboratories have been reported by *White* (54). Developed chromatographic methods for the determination of antibiotics in biological materials are characterized by different types of detection, such as high-performance liquid chromatography (HPLC) methods with an electrochemical detection (ECD) (55), fluorescence detection (FLD) (56-60), ultraviolet (UV) detection (61-77) and mass spectrometry (MS) detection (78-97).

METHODS OF QUANTIFYING β-LACTAM ANTIBIOTICS IN BIOLOGICAL SAMPLES

Since the 1980s, literature on various methods of quantifying β-lactam antibiotics in biological samples has been available. Most of the methods developed, used chromatographic techniques such as high performance liquid chromatography with ultraviolet detection (HPLC-UV) and liquid chromatography with mass spectrometry detection (LC-MS). A numerous HPLC methods with UV detection were developed for quantification of β-lactam antibiotics, both for the quantification of individual representatives of beta-lactam antibiotics (12, 98-114) and for simultaneous quantification of several antibiotics from this group (2, 8, 57, 65, 76, 77,

115-127). More recent studies have used ultra high-performance liquid chromatography (UHPLC) as method for the determination of antibiotics, with UV-diode array detector (DAD) or photo diode array (PDA) (121, 128-133).

More recently, developed methods have used liquid chromatography tandem mass spectrometry (3, 92, 95, 134-136) and since recently, mass spectrometry, mostly in combination with UHPLC (UHPLC-MS/MS), has been used for detection (17, 88, 93, 94, 137-140). These methods have been developed for simultaneous determination of several antibiotics, mostly β-lactams, in different species of biological samples.

The other reported methods are non-chromatographic methods, like microbiological assay (MBA) (46, 141-145), electrophoresis (146-150), photometry (151), voltammetry (152), immunosensors (153), ELISA (154) or an enzymatic assay (155), for the determination of β-lactam antibiotics in biological samples.

METHODS OF QUANTIFYING MEROPENEM IN BIOLOGICAL SAMPLES

Determination of meropenem levels (concentration) in biological samples has been predominantly done by chromatographic methods (HPLC and UPLC) combined with UV detection (Table 1) and with MS detection (Table 2). There are methods for determination of only meropenem (12, 100, 102, 104-106, 110, 113, 170, 176, 178, 182, 183) and methods that can be used for simultaneous quantification from several antibiotic to ten (76, 93), twelve (95, 120, 137), fifteen (91) and even twenty-one antibiotic (86) in single run (marked with s in tables 1 and 2). Meropenem has been determined in various biological matrices, such as plasma, serum, urine, filtrate-dialysate, bile, sputum, cerebrospinal fluid (CSF), bronchoalveolar lavage fluid (BALF) and epithelial lining fluid (ELF), while the most common are samples plasma and serum.

The methods for determination of meropenem depending on biological matrices required different sample preparation techniques. The preparation of the plasma and urine sample consisting only of dilution and filtration of the sample was performed by *Burman et al.* (157) and *Nilsson-Ehle et al.* (158). Then, sample preparation techniques are very often used, such as simple precipitation of protein with organic solvents, like methanol (8, 29, 30, 77, 91, 93, 95, 133, 185), acetonitrile (2, 17, 76, 86, 88, 94, 102, 105, 118, 120, 121, 125, 127, 128, 134, 135, 138, 139, 162, 167, 175, 176, 178, 179, 180, 182, 183), a mixture of both (113, 177, 186), protein precipitation by acids, such as trichloroacetic acid (98) (Table 1 and 2). In the study *Paal et al.* (92), protein precipitating agents in different combinations has been tested, and the best extraction yields and reproducibility were obtained with a mixture of methanol-methyl-tert-butyl ether (90:10, v/v). *Kipper et al.* (29) consider different ways of preparing a sample of plasma and urine, pointing out the limitations and problems of sample preparation techniques. They conclude that the most suitable method of protein precipitation for meropenem plasma samples is methanol extraction, while filtration through syringe filters was a completely satisfactory method of sample preparation for analysis of meropenem in urine.

For extraction of meropenem from biological matrices have been also used sample preparation techniques without protein precipitation included solid phase extraction (SPE) with different sorbents such as C18 (105, 117, 132, 156, 160, 161, 166, 168, 170), C8 (159, 163, 164), Sep-Pak NH_2 (106), Strata-X (12) and Oasis® HLB (3) (Table 1 and 2). *Ohmori et al.* (3) have been reported an absolute recovery of meropenem of approximately 70% at extraction β-lactam antibiotics from plasma by Oasis® HLB sorbent. While *Colin et al.* (137) have been comparing the four different kinds of SPE material of Waters Oasis® (MCX, MAX, WAX and WCX) for extraction β-lactam antibiotics from a spiked plasma sample. They results was demonstrate that overall recovery was highest for the MCX sorbent, which has an average absolute recovery of meropenem 91.5 ± 2.4%. *Ferrone et al.* (132) were tested twelve different SPE materials for the extraction of meropenem and ciprofloxacin from human plasma, and the SilactSPE C18 (100 mg, 1 mL) cartridges gave the best extraction efficiency. About miniaturized form of the SPE technique was reported in a study *Ferrone et al.* (130) where is a semi-automated microextraction by packed sorbent (MEPS) for sample preparation in the determination of meropenem was used.

In order to increase the sensitivity of the method after SPE and sometimes after PP, it necessary evaporating the organic phase and the residue re-dissolved in mobile phase or buffer, that extends sample preparation time (3, 8, 29, 76, 94, 105, 107, 117, 121, 124, 127, 128, 132, 133, 171, 179). From other side, due to the propensity of protein precipitation extraction methods to matrix effects, protein precipitation with acetonitrile followed by a dilution in mobile phase simplified the extraction procedures and provided acceptable recoveries and matrix effect results (182). This procedure of sample preparation have been published in several studies (17, 86, 120, 139).

The liquid-liquid extraction (LLE) was also used for sample preparation in the determination of meropenem (2, 102, 172, 181, 184). This sample preparation technique allows removal of lipid-soluble components into the organic phase (dichloromethane or chloroform) and resulting aqueous phase showed a reduced chromatographic background at HPLC analysis (2, 109). In the study *Ferrari et al.* (183) samples preparation was performed using a commercially available extraction kit which needs a very small amount of sample (50 µl). New liquid-liquid microextraction (LLME) techniques have been reported, such as: air assisted dispersive liquid-liquid microextraction with solidification of the floating organic droplet (AA-DLLME-SFO) (131) and homogeneous liquid-liquid microextraction (HLLME) by (174).

Some methods of preparation required special equipment, like column switching (104), ultra-filtration (UF) (110, 122, 126, 173, 175) or HPLC-integrated sample preparation, where the on line extraction technique was realized by automatically switching from the extraction column to the analytical column (169). In the study *Zander et al.* (88) it was presented a semi-automated sample preparation included a manual protein precipitation step followed by two-dimensional ultra high-performance liquid chromatography (2D-UHPLC), which consisted of three steps: on-line sample clean up (on-line SPE), transferring the extracted sample to the analytical column including chromatographic separation and re-equilibration.

Most methods for separating meropenem have used reversed phase columns, like C18 (2, 30, 76, 86, 91, 106, 107, 122, 125, 127, 134, 139, 140, 173, 180, 181), C8 (92, 105, 117, 118), phenyl (88, 178), pentafluorophenyl (121, 129) and HILIC column (138, 184, 185). *Rehm & Rentsch* were first to describe method for the determination of imipenem, meropenem and cefepime using HILIC MS/MS, and possibility to measure simultaneously plasma and CSF samples (184).

Different mobile phases for elution of meropenem have been consisted of binary mixtures (buffer solution/acetonitrile or buffer solution/methanol) and ternary mixtures (buffer solution/acetonitrile/methanol), with a pH value of buffer solutions varied from 2.0 (120) to 7.4 (117) in a isocratic or gradient mode, especially when it is necessary to separate several antibiotics at once (Table 1 and 2). According to the results of most authors, it seems that binary mixtures of buffer solution with 5-15% solvent such as acetonitrile or methanol could be most suitable for elution of meropenem in biological samples. Depending on the LC apparatus (HPLC and UPLC) and chromatographic conditions (column types, mobile phase and pH, isocratic or gradient mode, flow rate) retention time for meropenem ranges from 2.3 min (172) to 22.5 min (118) for HPLC and from 1.05 (182) to 7.5 min for UPLC (128).

Table 3 shows several non-chromatographic techniques (analytical methods) have been reported for the determination of meropenem in biological fluids using microbiological assay (MBA), capillary electrophoresis and voltammetry. The major metabolite of meropenem (ICI 213,689) was determinited by radioimmunoassay (RIA) (142, 157, 188).

The validation of newly developed bioanalytical methods for the quantification of meropenem was carried out mostly according to the *Food and Drug Administration* (FDA) guidelines (2, 3, 29, 93, 117, 120, 122, 183, 189) and the European Medicines Agency (EMA) guidelines for bioanalytical method validation (127, 128, 181, 182, 184), which demonstrate that reliable for the intended applications.

ADVANTEGES AND DISADVANTAGES OF THE METHODS FOR DETERMINATION OF MEROPENEM

Advantages and disadvantages of the developed methods for determination of meropenem in biological samples we can divide into advantages and disadvantages of sample preparation procedures and advantages and disadvantages of instruments and equipment used for detection and quantification of antibiotics.

Microbiological assay by the agar diffusion method as most widely used method have many advantages over other methods: simplicity, low cost, the ability to test enormous numbers of microorganisms and antimicrobial agents, and the ease to interpret results provided, while main disadvantage of the test is the lack of specificity and the possibility of producing erroneous results when other unsuspected antibiotics are present (190).

There was a need for highly specific, sensitive and rapid method due to polyantimicrobial therapy in patients, low concentrations of drugs in biological fluids and rapid method because many antibiotics (e.g. β-lactams) have serious stability problems. This has made HPLC methods more favorable than other traditional microbiological methods.

Solid phase extraction (SPE) and precipitation of proteins (PP) with organic solvents are the most common techniques of sample preparation for analysis by chromatographic methods. SPE has many advantages in comparison with more classical techniques, such as high recoveries of the analyte and highly purified extracts, but is and an appropriate choice of sorbent is essential to efficiency of the SPE procedure. The disadvantage of this preparation technique is the longer sample preparation time, due to the need to evaporate the organic phase after extraction in order to provide the concentration of the analyte and increased the sensitivity of the method. PP with organic solvents is enables fast and easy preparation of sample, but the downside this preparation is the propensity to matrix effects. Therefore this method of preparation requires an additional step in the preparation such as dilution or additional extraction with an organic solvent (i.e. LLE) in order to reduce or eliminate matrix interference, which prolongs the sample preparation time. In some methods of analysis, sample preparation is automated and sample preparation time is greatly shortened. This is made possible by special equipment and apparatus, such as column switching, ultra-filtration (UF) and HPLC-integrated system, which are often not available to laboratories due to their high cost. Ultra-filtration (UF) is simple and effective extraction method providing the measuring of the free fraction and good recoveries of the drug but it expensive.

The chromatographic method based on HPLC-UV is a frequently applicable method in clinical laboratories because of its advantages, like simple and economic preparation of the samples and a more affordable equipment, while the disadvantages high sample volume (200-500µl), longer run

time, less specific and sensitive (high LOQ) compared to HPLC-MS/MS. Tables 1 and 2 show some of the main characteristics of the methods. Also less expensive methodology than mass spectrometry is ultra high-performance chromatography (UHPLC) with UV detector (DAD or PDA) which allows better performance, like faster run time and improved resolution and sensitivity compared with conventional HPLC-UV. While liquid chromatography methods with mass spectrometric detection (HPLC-MS/MS and UHPLC-MS/MS) have many advantages, such as short analysis time, small sample volume with minimal sample preparation and high specificity and sensitivity compared to previously applied analytical techniques. UHPLC-MS/MS techniques provides a shorter run time and sharper peak shape, which improves sensitivity and reduces potential interference by matrix components thus enabling simultaneous quantitative analysis of multiple analytes. The downside of mass detection chromatographic techniques is expensive instruments and additional equipment, so it is not available to all laboratories.

Capillary electrophoresis (CE) analytical methods developed for determining meropenem in biological samples has unique advantages and disadvantages with respect to sensitivity precision and simplicity of use. *Mrestani et al.* (146) have reported that in addition to ease of use and good repeatability, high sensitivity, the main advantages of the method is low amount of sample required and the relatively short analysis time. As for sample preparation, they deproteinized plasma samples with acetonitrile and used urine samples without pretreatment for analysis. CE methods with direct injection of serum (148), direct injection of cerebrospinal fluid and plasma sample was pretreated by means of SPE (187) have also been developed. Methods where measurement is enabled by direct injection of samples into the capillary provide fast, reliable, and economical analysis.

Table 1. Chromatographic methods (HPLC and UPLC) with UV detection for the quantification of meropenem in biological samples.

Biological sample	Volume of sample (µl)	Sample preparation	Mobile phase (Eluent)	RT of MER (min)	Run time (min)	LOD/LOQ	No. of ABs	Reference
Plasma Urine	100	SPE (C18)	5mM TBA phosphate / MeOH (88 / 12, v/v) for plasma 10mM phosphate (pH 7.4) / ACN (100 / 6, v/v) for urine	-	-	0.06 mg/l / -	1	Bax et al. (156)
Plasma Urine	-	Dilution and filtration	10mM phosphate (pH7.4) / MeOH (82 / 18, v/v) for plasma and (75 / 25, v/v) for urine	-	-	0.5 mg/l / - 5 mg/l / -	1	Burman et al. (157)
Plasma Urine	-	Dilution and filtration	10mM phosphate (pH 7.4) / MeOH (75 / 25, v/v) for plasma and (82 / 18, v/v) for urine	-	-	0.4 mg/l / - 4 mg/l / -	1	Nilsson-Ehle et al. (158)
Plasma Bile	100 50	SPE (C8)	50mM phosphate / MeOH (85 / 15, v/v) for plasma 57mM phosphate (pH 7) / MeOH (85 / 15, v/v) for bile	5-5.5	-	0.1 mg/l / - 0.3 mg/l / -	1	Granai et al. (159)
Plasma Urine	100 50	SPE (C18)	5mM TBA phosphate / MeOH (88 / 12, v/v) for plasma 10mM phosphate (pH 7.4) / ACN (100 / 6, v/v) for urine	~9 ~5.5	-	0.2 µg/ml / - 0.6 µg/ml / -	1	Harrison et al. (160)
Plasma Urine	-	SPE (C18)	5mM TBA phosphate / MeOH (85 / 15, v/v) for plasma 0,1% phosphoric acid in water for urine	-	-	- / 0.5 µg/ml - / 1.0 µg/ml	1	Bedikian et al. (161)

Biological sample	Volume of sample (µl)	Sample preparation	Mobile phase (Eluent)	RT of MER (min)	Run time (min)	LOD/LOQ	No. of ABs	Reference
Plasma	500	PP (TCA)	ACN / water / glacial acetic acid (21.2 / 78/ 0.8, v/v/v)	3.9	-	25 ng/ml / -	1	Al-Meshal et al. (100)
Serum	-	PP (ACN)	MeOH / phosphoric acid / water (25% / 1% / 74%)	-	-	-	1	Lovering et al. (162)
Plasma Urine	100 10-50	SPE (C8)	50mM phosphate (pH 7) / MeOH (85 / 15, v/v) for plasma 50mM phosphate (pH 7) / ACN (100 / 7, v/v) for urine	-	-	0.1 mg/l / - 5 mg/l / -	1	Kelly et al. (163)
Plasma Bile, Urine, CSF, AH, Blister fluid	-	SPE (C8)	50mM phosphate (pH 7) / MeOH (85 / 15, v/v) for plasma 50mM phosphate (pH 7) / ACN (100 / 7, v/v) for bile, urine, CSF, aqueous humour, blister fluid	~5.5 ~4.5	-	-	1	Hutchison et al. (164)
Rat plasma	50	Column switching	50mM phosphate (pH 7) / ACN (94% / 6%)	6.5	< 20	0.1 µg/ml / -	1	Lee et al. (165)
Serum	500	PP (ACN, DCM)	10mM acetate (pH 4) / ACN (95 / 5, v/v)	5.2		- / 0.25µg/ml	1	Elkhaïli et al. (102)
Rat plasma	100	SPE (C18)	10mM acetate (pH 4.8) / MeOH (85 / 15, v/v)	7.3	15	- / 0.125mg/l	1	Dupuis et al. (166)
Plasma Serum	-	PP (ACN)	10mM 1- heptane-sulphonic acid / ACN, (92 / 8, v/v)	8.3	-	2 mg/l / -	3s	Ip et al. (167)
Serum	10	On line-SPE, column switching	10mM phosphate (pH 7), 5mM $TBAHSO_4$ / MeOH (70%/30%)	4.2	-	0.1 µg/ml / -	1	Bompadre et al. (104)
Plasma	500	SPE (C18) and evaporation	12.5mM phosphate (pH 6) / ACN (96.2 / 3.8, v/v)	5.4	-	- / 0.02µg/ml	1	Farin et al. (105)
Plasma BAL, EFL	-	SPE (C18)	50mM acetate (pH 5) / ACN (90 / 10, v/v)	-	-	50 ng/ml / - 1.25ng/ml / -	1	Allegranzi et al. (168)
Serum Sputum	20 or 100	Column switching	50mM phosphate (pH 5) / ACN (95 / 5, v/v)	-	30	- / <0.5 µg/ml	2	Ehrlich et al. (169)
Serum Urine	500 2000	SPE (Sep-Pak NH_2)	15mM phosphate / ACN / MeOH (84 /12 / 4, v/v/v), pH 2.8	7.47	< 8	108 ng/ml / -179 ng/ml / -	1	Özkan et al. (106)
Plasma Filtrate-dialysate	400	SPE (C18) and evaporation	5mM TBA chloride (pH 7.4) / MeOH, gradient elution	13.8	27	1.2 / 2.5 µg/ml	1	Robatel et al. (170)
Plasma	200	UF	10mM phosphate (pH 7.4) / ACN (90 / 10, v/v)	3.8	7	0.01/0.05 µg/ml	1	Ikeda et al. (110)
Plasma	500	SPE (C18) and evaporation	1/15M phosphate (pH 7.4) / ACN, gradient elution	17.8	30	- / 0.5 µg/ml	5s	Denooz & Charlier (117)

Biological sample	Volume of sample (µl)	Sample preparation	Mobile phase (Eluent)	RT of MER (min)	Run time (min)	LOD/LOQ	No. of ABs	Reference
Plasma	100	PP (ACN) and evaporation	100mM phosphate (pH 6.8) / MeOH, gradient elution	22.5	25	- / 0.5 mg/l	3s	Legrand et al. (171)
Plasma Urine	-	PP (MeOH) and evaporation	50mM phosphate (pH 3) / ACN / MeOH (86 / 12 / 2, v/v/v)	4.8	-	0.05/0.1 µg/ml 0.5 / 1 µg/ml	1	Kipper et al. (29)
Serum	250	PP (ACN/MeOH, 1:1, v/v), dilution	0.5% FA in water / 0.25% FA and 4.75% water in ACN, gradient elution	7.7	15	1 / 3 mg/l	1	Bias et al. (113)
Serum	500	PP (ACN, DCM)	5mM sodium 1-octanesulfonate monohydrate (pH 3) / ACN (79% / 21%)	2.3	4	-	4	Delattre et al. (172)
Peritoneal fluid Bile	400	UF	10mM phosphate (pH 7.4) / ACN (100 / 10, v/v)	5.5	-	- / 0.05 µg/ml - / 0.1 µg/ml	1	Kameda et al. (173)
Plasma	200	PP (ACN, Chloroform)	50mM phosphate (pH 2.4) / ACN (92% / 8%)	2.4	-	- / 5 µg/ml	12 (4s)	McWhinney et al. (2)
Plasma	100	PP (ACN) and dilution	10mM phosphoric acid solution (pH 2) / ACN, linear gradient	4.8	22	<1 / 2 µg/ml	12s	Verdier et al. (120)
Plasma	200	PP (ACN) and evaporation	100mM phosphate (pH 7) / MeOH, gradient elution	~6.2	7	- / 0.5 mg/l	4s	Dailly et al. (121)
Plasma	200	UF	50mM phosphate (pH 2.4) / ACN (92% / 8%)	3.1	-	- / 0.1 µg/ml	10 (3s)	Briscoe et al. (122)
Serum	200	PP (MeOH) and evaporation	50mM phosphate (pH 3.8) / ACN, gradient elution	7.3	18	- / 2 µg/ml	6s	Wolff et al. (8)
Plasma	100	PP (ACN) and evaporation	100mM phosphate (pH 7) / MeOH (87% / 13%)	7.5	-	- / 0.5 µg/ml	1	Casals et al. (128)
Bacterial growth medium	100	PP (ACN, MeOH) and evaporation	water with 0.1% TFA / ACN : water 40:60 (v/v) with 0.1% TFA, gradient elution	~7.8	14	- / 0.5 µg/ml	3s	Wicha & Kloft (124)
Serum	200	SPE (Strata-X)	100mM TRIS/HCl buffer (pH 8.5) and 15% MeOH	7.8	10	- / 3.5 mg/l	1	Roth et al. (12)
Plasma	200	PP (ACN)	0.2% phosphoric acid (pH 2.2) / ACN, gradient elution	5.0	15	- / 2 µg/ml	4s	Pinder et al. (125)
Plasma	50	MEPS	10mM acetate (pH 4) / ACN - MeOH (80 / 20, v/v), gradient elution	1.55	5	- / 0.02 µg/ml	3s	Ferrone et al. (130)
Plasma	2000	PP (TCA/ZnSO4, 60/40,v/v), AA-DLLME-SFO	10mM acetate (pH 4) / ACN - MeOH (80 / 20, v/v), gradient elution	1.76	5	- / 2 µg/ml	5s	Ferrone et al. (131)

Biological sample	Volume of sample (µl)	Sample preparation	Mobile phase (Eluent)	RT of MER (min)	Run time (min)	LOD/LOQ	No. of ABs	Reference
Plasma	1000	SPE (C18) and evaporation	10mM acetate (pH 3) / ACN - MeOH (80 / 20, v/v), gradient elution	1.55	< 5	0.004 / 0.02 µg/ml	2s	Ferrone et al. (132)
Plasma Serum	200	HLLME	0.5% FA / ACN, (30% / 70%)	-	-	0.03 / 0.1mg/l	1	Cherkashina et al. (174)
Serum	500	PP (MeOH)	1.75mM acetic acid solution / MeOH, gradient elution	5.3	8	0.057 / 0.192 µg/ml	1	Dincel et al. (30)
Plasma	250	PP (ACN) and evaporation	100mM phosphate (pH 3.15) / MeOH, gradient elution	11.3	30	0.08 / 1.0 µg/ml	4s	Milla et al. (127)
Plasma	100	PP (ACN) and evaporation	0.35% phosphate (pH 7) / ACN, gradient elution	3	8	0.5 / 1.0 µg/ml	10s	Cairoli et al. (76)
Murine plasma	200	UF	25mM phosphate (pH 6.5) / MeOH (87% / 13%)	3.6	16	- / 0.25 µg/ml	2s	Sutherland & Nicolau (126)
Plasma, ISF	100	PP (ACN), UF	100mM phosphate (pH 2.9-3.1) / ACN (92 / 8, v/v)	2.5-4.5	-	- / 0.1 mg/l	1	Simon et al. (175)
Serum	200	PP (MeOH) and evaporation	105mM phosphate (pH 5) / ACN, gradient elution	6.25	22	- / 0.25 mg/l	8s	Fage et al. (133)
Serum	100	PP (MeOH)	50mM phosphate (pH 6.9) / ACN, gradient elution	8.0	17	0.18 / 0.66 mg/l	6s	Roth et al. (77)

RT – retention time; MER – meropenem; LOD - limit of detection; LOQ - limit of quantification; No. of ABs – number of antibiotics analyzed simultaneously; PP – protein precipitation; SPE – solid phase extraction; UF – ultra-filtration; MEPS - microextraction by packed sorbent; MEPS - microextraction by packed sorbent; AA-DLLME-SFO - air assisted dispersive liquid-liquid microextraction with solidification of the floating organic droplet; HLLME - homogeneous liquid-liquid microextraction; ACN – acetonitrile; MeOH – methanol, FA - formic acid; DCM – dichloromethane (methylene chloride); TBA - Tetrabutylammonium; TCA - trichloroacetic acid; TFA - trifluoroacetic acid; TRIS - tris(hydroxymethyl)aminomethane; CSF - cerebrospinal fluid; ELF - epithelial lining fluid; BAL - bronchoalveolar lavage; ISF - interstitial fluid; AH - aqueous humour;

Table 2. Chromatographic methods (HPLC and UPLC) with tandem MS detection for the quantification of meropenem in biological samples.

Biolog-ical sample	Volume of sam-ple (µl)	Sample preparation	Mobile phase (Eluent)	RT of MER (min)	Run time (min)	LOD/LOQ	No. of ABs	Refer-ence
Serum CSF	50	PP (ACN)	5mM ammonium ace-tate / ACN, (78/22, v/v)	-	-	-/0.02 µg/ml -/0.004µg/ml	1	Nau et al. (176)
Plasma, BALF, ACs, ELF	20 150, 200	PP (ACN/MeOH, 50:50, v/v)	-	-	-	-/0.5 µg/ml -/1.0 ng/ml	1	Conte et al. (177)
Plasma	100	PP (ACN)	5mM ammonium ace-tate / ACN, (78/22, v/v)	0.9	-	-/0.02 mg/l	1	Krueger et al. (178)

Biological sample	Volume of sample (µl)	Sample preparation	Mobile phase (Eluent)	RT of MER (min)	Run time (min)	LOD/LOQ	No. of ABs	Reference
Plasma	50	PP (ACN) and evaporation	0.1% FA in water / 0.1% FA in MeOH, gradient elution mode	1.13	3.5	-/0.2 mg/l	7s	Ahsman et al. (179)
Serum	50	SPE (Oasis® HLB) and evaporation	10mM ammonium formate with 0.1% FA / MeOH with 0.1% FA, gradient elution	5.11	13	0.05/0.1µg/ml	8s	Ohmori et al. (3)
Plasma	50	PP (ACN)	0.1% FA in water / 0.1% FA in MeOH, gradient elution	1.72	6	- /100 ng/ml	6s	Cohen-Wolkowiez (180)
Plasma	20	PP (ACN, DCM)	0.1% FA in water / 0.1% FA in ACN, gradient elution	2.07	5.5	- /0.5 mg/l	7s	Carlier et al. (181)
Plasma	50	SPE (Oasis®MXC)	1mM ammonium acetate with 5% ACN / ACN, gradient elution	~1.7	5	- / 0.43 µg/ml	12s	Colin et al. (137)
Plasma	300	PP (ACN)	0.1% FA in water / 0.1% FA in ACN, gradient elution	3.4	7	- / 0.1 µg/ml	7s	Sime et al. (134)
Plasma Urine Filtrate-dialysate	50	PP (ACN) and dilution	0.1% FA in water / 0.1% FA in ACN, gradient elution	1.05	3	- /0.27 mg/l - /0.24 mg/l - /1.22 mg/l	1	Rigo-Bonnin et al. (182)
Urine Serum CSF Bronchial aspirat.	500 1000 200 1000mg	PP (ACN) and dilution	0.01% FA in water / MeOH, gradient elution	1.09-1.29	< 6	0.1/0.5 mg/l 0.2 /0.5 mg/l 0.2 /0.5 mg/l 0.2 /0.5 mg/l	21s	Cazorla-Reyes et al. (86)
Plasma	15	PP (ACN) and dilution	2mM ammonium acetate with 0.1% FA in water / 2mM ammonium acetate with 0.1% FA in MeOH, gradient elution	< 1.5	2.5	- / 0.5 mg/l	5s	Carlier et al. (17)
Serum	50	PP (ACN), on line-SPE (Oasis® HLB)	[water/ FA, 99.9/0.1 (v/v)] / [MeOH / ACN 75/25 (v/v)], gradient elution	2.22	5	- / 0.25 mg/l	6s	Zander et al. (88)
Plasma	100	PP (ACN) and dilution	0.1% FA in water / 0.1% FA in ACN, gradient elution	1.12	7	- / 0.5 mg/l	9s	Rigo-Bonnin et al. (139)
Plasma	10	Dilution and PP (ACN)	10mM ammonium formate with 0.1% FA (pH 3.5) / MeOH with 0.1% FA, gradient elution	4.17	6.6	0.05 / 1 µg/ml	1	Martens & Bode Böger (188)

Biological sample	Volume of sample (µl)	Sample preparation	Mobile phase (Eluent)	RT of MER (min)	Run time (min)	LOD/LOQ	No. of ABs	Reference
Plasma	50	PP (ACN)	100mM ammonium formate (pH 6.5) / ACN, (20/80, v/v)	2.45	5.2	- / 0.2 µg/ml	9s	Abdulla et al. (138)
Plasma	100	PP (MeOH) and dilution	2mM ammonium formate with 0.1% FA in water / ACN with 0.1% FA, gradient elution	3.45	9	- / 0.03 mg/l	15s	Lefeuvre et al. (91)
Serum	100	PP (MeOH/MTBE, 90:10, v/v)	10mM ammonium formate in water-FA, 99.9:0.1 (v/v) / ACN	1.81	4	- / 0.25 mg/l	6s	Paal et al. (92)
Plasma	40	PP (MeOH) and dilution	2mM ammonium acetate with 0.1% FA in water / 2mM ammonium acetate with 0.1% FA in MeOH, gradient elution	1.69	4	- / 0.1 mg/l	10s	El-Najjar et al. (93)
Serum	50	PP (ACN) and evaporation	5mM ammonium acetate (pH 2.4) / 0.1% FA in ACN, gradient elution	1.20	4	- / 0.1 mg/l	7s	Magréault et al. (94)
Plasma RRTE	10	Dilution and PP(ACN)	0.1% FA in water / 0.1% FA in ACN, gradient elution	1.6	5.5	0.01/0.05 µg/ml	2s	Parker et al. (135)
Plasma	50	Extraction kit and dilution	0.1% FA in water / 0.1% FA in MeOH, gradient elution	2.72	7	- / 1 mg/l	4s	Ferrari et al. (183)
Plasma	100	PP (MeOH) and dilution	10mM ammonium formate with 0.4% FA / ACN, gradient elution	2.6	< 9	- /0.05 µg/ml	12s	Decosterd et al. (95)
Plasma CSF	50	PP (MeOH), online extraction	10mM ammonium acetate with 0.1% FA / ACN-MeOH (1:1,v/v) with 10mM ammonium acetate and 0.1 % FA	4.7	13	- / 0.4 mg/l	3s	Rehm & Rentsch (184)
Plasma	10	PP(MeOH/ACN/H_2O, 6:2:2, v/v/v)	0.1% FA in water / 0.1% FA in MeOH-ACN (8:2,v/v), gradient elution	1.38	2.7	0.04/0.2 mg/l	3s	Krnáč et al. (185)

RT – retention time; MER – meropenem; LOD - limit of detection; LOQ - limit of quantification; No. of ABs – number of antibiotics analyzed simultaneously; PP – protein precipitation; SPE – solid phase extraction; UF – ultra-filtration; ACN – acetonitrile; MeOH – methanol; FA - formic acid; MTBE – methyl tert-butyl ether; CSF- cerebrospinal fluid; BALF-bronchoalveolar lavage fluid; ELF-epithelial lining fluid; ACs-alveolar cells; RRTE - renal replacement therapy effluent;

Table 3. Non-chromatographic methods for the quantification of meropenem and its metabolite ICI 213,689 in biological samples.

Techniques	Biological sample	Reference
MBA	Plasma, blister fluid	Wise et al. (141)
MBA	Plasma, urine	Leroy et al. (142)
MBA	Plasma, urine, dialysate	Chimata et al. (143)
MBA	Serum, bronchial secretions	Bergogne-Berezin et al. (144)
MBA	Plasma	Al-Meshal et al. (100)
MBA	Plasma, tissue, blister fluid	Hutchison et al. (164)
MBA	Serum, tissues	Byl et al. (145)
CE	Plasma, urine	Mrestani et al. (146)
CE (MEKC)	Serum	Kitahashi & Furuta (148)
CE (MEKC)	Plasma, CSF	Chou et al. (186)
Voltammetry	Plasma	Jhankal & Sharma (152)
RIA	Plasma, urine	Burman et al. (157)
RIA	Plasma	Leroy et al. (142)
RIA	Plasma, urine	Christensson et al. (187)

MBA -. microbiological assay; CE- capillary electrophoresis; MEKC - micellar electrokinetic capillary chromatography;RIA - radioimmunoassay

CONCLUSION

Timely information on meropenem concentrations in biological samples of patients facilitates monitoring of meropenem in clinical routine, which would allow quick adjustment of therapy and a higher probability of eradicating the infection as well as reducing the possibility of overdose and drug microbial resistance. Therefore, it is very important to apply an appropriate method for measuring the concentration of meropenem.

This review article summarizes the current knowledge of methods for determination the concentration of meropenem in different biological samples. Provides information on various sample preparation techniques, use of apparatus and equipment, as well as information on the advantages and limitations of the methods.

In the future, the development of new methods of quantification of meropenem and other antibiotics should continue in the direction of even simpler sample preparation by reducing the preparation steps with the use of more suitable reagents and avoiding complex and lengthy preparation procedures. In addition, equipment and apparatus for measuring meropenem concentrations should be sensitive, easy to handle and inexpensive. This would result in an even faster, more sensitive, selective, reliable, and accessible method for determining meropenem in biological samples.

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