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A Subject Review on Some Analytical Methods for Determination of Fosfomycin Drugs

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Abstract

Medicines comprising fosfomycin are prescribed for urinary tract infections. These drugs are available for oral use as tromethamine and calcium, while fosfomycin-sodium and disodium are given for intravenous (IV) and intramuscular (IM). Many quantitative analytical methods have been reported to estimate Fosfomycin in blood, urine, plasma, serum, and pharmaceutical dosage formulations. Some techniques were spectrophotometric, mass spectrometry, gas chromatography, high-performance liquid chromatography, and electrochemical methods. Here we perform a rapid narrative review that discusses and comparison between them of various analytical methods for the determination of Fosfomycin-containing drugs.

Keywords: Review, Fosfomycin, Drugs, Medicines.

1. Introduction

Fosfomycin (Fig.1) is a broad-spectrum antibiotic that inhibits the phosphoenol pyruvate transferase enzyme involved in the synthesis of peptidoglycan (found in the cell wall of Gram-positive and negative bacteria)[1,2]. S. aureus, staphylococci, penicillin-resistant S. pneumonia, Enterococcus species, Escherichia coli (E. coli), Klebsiella pneumonia, Citrobacter, and N. meningitides are often referred to as meningococcus, in addition to

Enterobacteriaceae and carbapenemase strains[3,4]. This drug's intravenous (IV) is widely prescribed in combination with other antimicrobial agents; it has an excellent safety profile with long-term administration[5]. This naturally occurring antibiotic agent was discovered in 1969[6].

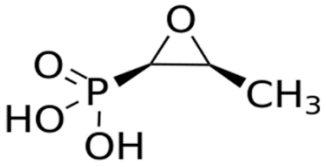

Figure 1. Chemical structure of Fosfomycin

The first chemical synthesis (**Figure 2**) was described by (Christensen, B. G.) et al. in 1969, based on epoxidation of the cis-Propenylphosphonic acid since diverse synthesis (chemical synthesis) of this drug has been described. Currently, there are three stages[6].

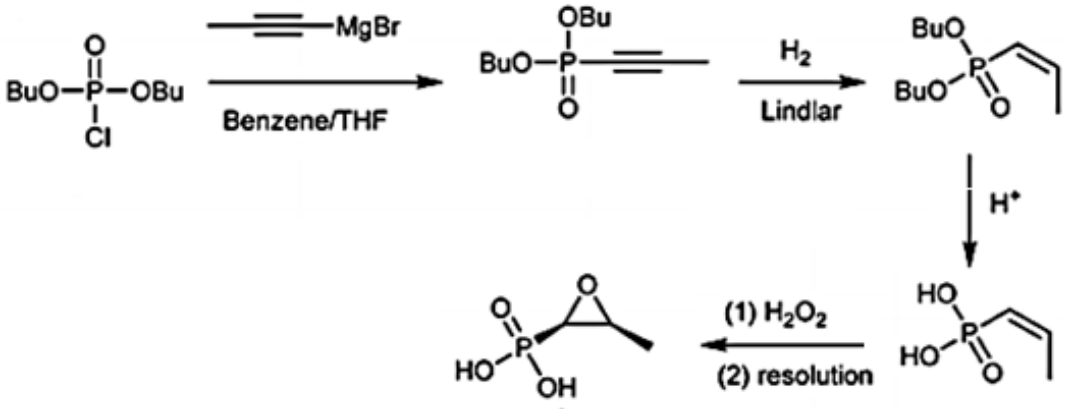

Figure 2. The first chemical synthesis of Fosfomycin

2. Results and Discussion

This literature review demonstrated various analytical methods for the quantitative determination of fosfomycin[7–32]. Many of these techniques were reported, as shown in (Table 1) below. Now Fosfomycin has been used to treat particularly urinary infections that occur from bacteria. Furthermore, fosfomycin differs from other antibiotics that are non-cross-resistance for Fosfomycin indicated in clinical application[33].

There was research to estimate fosfomycin in pharmaceutical preparations or biological fluids. HPLC methods were used utilizing different mobile phases of several solvents with different degrees of dilution having diverse columns. The first method used to determine the above drug in urine in 1970 was Thin-layer paper and gas-liquid chromatography with linearity ranging from (1-5)µg [7]. Also, it was found that the minimum linearity range for determining fosfomycin was (0.01-0.4) µg.mL-1 in chicken muscle, liver, and kidney using HPLC-MS/MS [23]. The highest linearity was over (50-5000) µg.mL-1 for determining fosfomycin in urine using capillary gas chromatography[14] with varying detection limits. It was also noted that the spectrophotometric methods were not widely used for assaying the above drug. Mostly, the simple chemical structure of the drug led to not being able to react with different reagents to estimate it in the visible region of the spectrum. It was observed that there were three methods

for the spectrophotometric determination of fosfomycin; the first method was at the visible region, λmax = 605 nm, with a specific absorptivity of 4.59 x 104 L. mol-1.cm-1 and linearity = (0 - 28 x 10- 6)M [15]. However, it has been estimated within the ultraviolet region at λmax = 254 nm, with specific absorptivity equal to (4.59 x 104 L.mol1-.cm-1 and its linearity = (30-70) µg.mL-1. In addition Flow Injection Spectrophotometric method used for determination of it in urine at visible region, λmax = 960 nm, Linearity = (3x10-6- 6x10-4) mol.L-1, T = 90°C, r = 0.9969, LOD= 1x10-6, RSD =1.2%, flow- rate = 0.2 mL.min-1. The drug is currently widely used to treat urinary tract infections with only one dose in the form of oral granules.

Table 1. Some analytical methods for the determination of Fosfomycin

Methods	sample	Results	Years	Ref. No.
Thin-layer, paper and gas-liquid chromatography	Urine	Linearity= (1-5)µg, R_F =(0.16-0.86), preparative PC crude (30-5o)%, TL plates loaded up to 150 µgof drug in (2-5) µL	1970	7
Specific ion monitoring method	Blood and urine	Linearity= (0.5-10) and (0.25-50) µg.mL^{-1}for microbiological and Sim methods respectively, Total Re. 25-28.1	1981	8
Gas chromatography	Biological and bacterial culture medium	apillary column OV 17-01, LOD = 1µ.mL^{-1}, assay of 100 microliters.	1987	9
anion-exchange chromatography	Plasma	λ max = 272 nm, leanirity(5-100)µg.mL^{-1}, mobile phase, is 0.4 mM of phthalate-buffer (pH =8.5), r= 0.999, RSD =(0.6-5.3)	1993	10
capillary zone electrophoresis	Serum	Linearity(10-100) µg. mL^{-1}, Re.=(0.5-18)%, RSD < 2%, buffer mobile phase (200 mM sodium borate + 10 mM phenylphosphonic acid)	1993	11
High performance liquid Chromatography	Plasma	Linearity = (10-80µg.mL^{-1}), IC-Pak, column (4.6x50) mm, pH =8.5, mobile phase acetonitrile: borategluconate v/v (12:88), r=0.999.	1993	12
Capillary electrophoresis	Serum and cerebrospinal fluid	Linearity = (2.5-200) µg/mL^{-1}, LOD = (1.0- 2.5 µg. mL^{-1}) in serum and aqueous fluids respectively, r= 0.999, SD = 94.5%.	1994	13
Capillary gas chromatography	Urine	Linearity=(50-5000)µg.mL^{-1}, LOD equal 10 µg. mL^{-1} , CV = 0.006, r = 0.999	1996	14
spectrophotometric method	pharmaceutical manufacture	λ max = 605 nm, E= 4.59x10^4 L. mol^{-1}.cm^{-1}, Linearity = (0-28x10^{-6})M.	1999	15
Gas chromatography	Plasma	Commercial Complexes of Drug(CCd) : a levorotatory, Ca (-) salt, a racemic, Ca (+/-) salt, and (THAM) salt.	1999	16
Gas chromatography	Chicken plasma	Linearity=(1-150)µg.mL^{-1}, column: HP-5 capillary, detector: flame ionisation (FID)LOD and LOQ = (1 and 2.1) µg mL^{-1} respectively, Re. 109%. R^2 =0.997, CV= (2.8 and 5.1).	2001	17
Flow Injection Spectrophotometric	Urine	λ max = 960 nm, Linearity = (3x10^{-6}- 6x10^{-4}) mol.L^{-1}, T = 90°C, r = 0.9969, LOD= 1x10^{-6}, RSD=1.2%, flow- rate = 0.2 mL.min^{-1}.	2002	18
Capillary electrophoresis analysis	Biological fluids	λ max = 254 nm, Linearity = (3.5 or 6.8-1000)mg./mL, LOD= (0.62-2), LOQ= (2.0-6.8) µg.mL^{-1}, RSD=(3.2-5.6), R> 0.9994.	2004	19

capillary zone electrophoresis	Pus	λ max = 254 nm, Linearity =(20 -7800) mg/mL/, LOD = 4.5 LOQ = 15, RSD = (2.4-8.2)%,, Re.= (75.4-90.0)%, R= 0.9956.	2005	20
liquid chromatographic/tandem mass spectrometric	Plasma	Column, ultimate XB-CN, Linearity = (0.1-12) mg .mL^{-1}, LOD < 0.02 µg.mL^{-1}, RSD = (2.4-8.2)%, Er. = (1- 4.2)%, R<10.6%.	2007	21
High performance liquid chromatography/tandem mass spectrometry	Chicken serum	Linearity(0.1-50)mg.mL^{-1}, column (150x4.6) mm, mobile phase, (20:80)% acetonitrile : water, Re. (95 to 108)%, Er.= (-7-7.8)%, CV. < 10%, Sd =(0.001-0.006).	2011	22
High performance liquid Chromatography	Chicken Muscle, Liver and Kidney	Con. Rang (0.1-0.28)µg.g^{-1}, CV.=(0.23-15.1)%, Re. = (81106%, 92-102% 99-107% for muscle, liver and kidney respectively, Er. = (0.3-3.76)%, LOQ=0.1 µg.mL^{-1}.	2011	23
liquid chromatography–tandem mass spectrometry	Plasma	Linearity =(50 -1200) ng.mL^{-1}, column ACE, 150 mm × 4.0 mm, mobile phase acetonitrile: water (30:70)%, RSD =(2.2-6.7)%, r^2 > 0.999, LOQ = 50ng.mL^{-1},	2014	24
High performance liquid Chromatography	Urine, Plasma	Linearity =(1 -2000), and (0.1-10) µg/mL, Re. = (68, 72%), precision (4.7%, 3.1%), accuracy (1.7% and 1.2%) for plasma and urine respectively.	2014	25
High performance liquid Chromatography	Plasma	Linearity = (5.000–2000) µg.mL-1, column, (2.1 x 50 mm), 5.0 µm, accuracy = (0.1- 3.9) %, precision =(2-8.2)%, Re. = 83.6%, limits of agreement (-2.6-30.6%). RSD =(2.2-6.7)%, R^2 = 0.9998, LOQ = 0.75µg.mL-1.	2015	26
liquid chromatography–tandem mass spectrometry	Plasma	Linearity = (15-150) and (100-750) µg/ml, column HILIC (150 × 2.1) mm x 5 m, with the precision =(4.0-6.4)% and (2.0–11.0)%, accuracy = (-1.1- 11.5) % and (0.6–7.8)%, R = 0.9976 and 0.9969.	2015	27
High performance liquid Chromatography	Urine, Plasma	Linearity =(0.75–375) µg.mL-^{1}, column HILIC, column 1.7µm, (2.1×100)mm, ,accuracy = (2.1- 3.2) %, precision =(1.5% -1.7)%, Re. = (99-103)%, RSD =(2.2-6.7)%, R^2 = 0.9998, LOQ = 0.75µg.mL^{-1}.	2017	28
High performance liquid Chromatography	Urine, aqueous fluids, plasma	Column, PS C18, Linearity: (12.5-800µg/mL), (62.5-4000µg/mL), (1-160µg/mL) for plasma, urine and aqueous fluid respectively, LOQ= plasma (≤ 6.5%, ≤ 8%), urine, (≤ 5.80, ≤ 6.30) %, and aqueous fluid (≤ 10.6, ≤12) %.	2017	29
High performance liquid Chromatography	Lysogeny broth (antimicrobial resistance)	Linearity = (1-1000)µg.mL^{-1}, column Kinetex (2.1 × 50) mm, 2.6 µm, (pH 4.76), precision <15%, accuracy (±85 and 115%).	2018	30
Liquid Chromatography Electrospray Ionization Mass Spectrometry	Plasma and Dialysate	Linearity = (25.0 – 700) µg. mL^{-1}, precision, (1.1-1.2%), accuracy (5.9% to 0.9%) respectively, Recovery ≥87%, Matrix effects (2.2- 4.3)%, R^2=0.999.	2021	31
spectrophotometric method	pharmaceutical manufacture	λ max = 254 nm, E= 4.59x104 L. mol-1.cm-1, Linearity = (30-70) µg.mL^{-1}, recovery was (98.75-101.00)%, RSD = 0.41%.	2021	32

3. Conclusions

Fosfomycin has a versioning mechanism of great action, lower toxicity, wide antibacterial activity, and excellent pharmacokinetic properties, in addition to its bioavailability [33]. An important literature review of different quantitative analytical methods for estimating fosfomycin in its pharmaceutical preparations was obtained. Many instrumental methods for determining fosfomycin have been developed, such as spectrophotometry, liquid chromatography with mass spectrometry, high-performance liquid chromatography (HPLC), ultra-performance liquid chromatography, and gas chromatography. However, chromatographic methods are the most used for quantitative analysis of these drugs in pharmaceuticals because these methods provide precise and accurate results.

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