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REVIEW ARTICLE

Analytical chemical techniques for the determination of Meloxicam: A review

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ABSTRACT

This review discusses the analytical methods used to quantify meloxicam (MLX). It comprehensively surveys the accuracy of current techniques, including spectrophotometry, chromatography, electrochemistry, and other techiques, for meloxicam (MLX) determination. These well-established methods have been successfully applied to diverse sample types, such as pharmaceutical formulations and biological samples like plasma and muscle. A nonsteroidal anti-inflammatory medication (NSAID) called meloxicam MLX commonly prescribed for the management of pain and inflammation associated with various arthritic conditions, is available in multiple formulations, including injections, tablets, and gels. Classified as a derivative of oxicam and structurally related to piroxicam, meloxicam (MLX) belongs to the enolic acid class of compounds developed by Boehringer Ingelheim. Marketed under the trade name Mobic, its properties are similar to those of aspirin as an analgesic.

Keywords: meloxicam (MLX), pharmaceuticals, biological samples, analytical methodologies

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1. Introduction

Meloxicam (MLX), chemically known as "4-hydroxy-2-methyl-N-(5-methyl-2-thiazolyl)-2H-1,2-benzothiazine-3-carboxamine-1,1-dioxide" (**Figure 1-A**)[1]. MLX acts as a non-steroidal anti-inflammatory medication (NSAID) that preferentially inhibits COX-2, providing pain and fever relief. While its main action is suppressing COX-2, it also affects COX-1, which might lead to gastrointestinal side effects[2-4]. MLX is used to treat osteoarthritis, rheumatoid arthritis, lower back pain, mastitis, pneumonia, and musculoskeletal disorders, including in veterinary medicine[5,6]. Its contain enolic acid compounds[7,8]. At physiological pH, MLX exhibits limited aqueous solubility[9]. MLX undergoes extensive hepatic metabolism, resulting in the formation of four pharmacologically inactive metabolites. These metabolites include the 5'-carboxy metabolite (acidic metabolite, **Figure 1-B**), the metabolites from the side chain cleavage product and the 5'-hydroxymethyl metabolite (alcoholic metabolite, **Figure 1-C**). All four metabolites are excreted in both urine and fece[4]. When used at or below he approved daily dosage of 15 mg, MLX has shown no known link to cardiovascular toxicity[2]. MLX Profile is shown in (**Table 1**)[10]. Marketed Formulations are shown in **Table 2** and elemental analysis shown in (**Figure 2**)[3]. The purpose of this review is to provide a general overview of the various approaches to MLX

determination, using different analysis techniques such as spectrophotometry, chromatography, and electrochemistry, and to assess these analytical chemistry techniques.

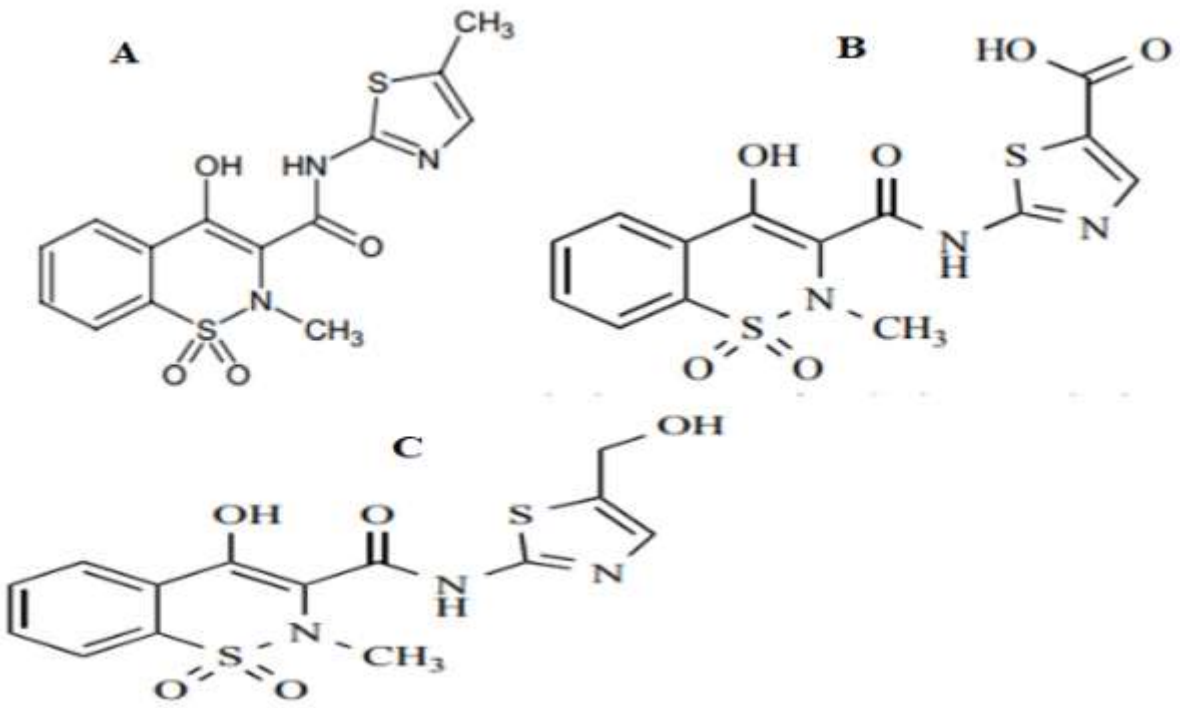

Figure 1. A- Chemical structure of MLX, B- Chemical structure of 5′-Carboxy MLX, C- Chemical structure of 5′-Hydroxy MLX.

Table 1. Profile of MLX.

name of chemical	**"4-hydroxy-2-methyl-N-(5-methyl-2-thiazolyl)-2H-1,2-benzothiazine-3-carboxamine-1,1-dioxide"**
Chemical formula	$C_{14}H_{13}N_3O_4S_2$
Molecular weight	351.40 g/mol
Melting point	254 °C
Solubility Organic Solvents	(DMSO & Dimethyl formamide)
Half life	20 hrs
Pka value	1.1 & 4.2
Log P value	3.34

Table 2. Marketed Formulations of MLX.

Dosage form	**Marketed formulation**	**How to take**
Oral Suspension	Metacam© (1.5 mg/mL)	With or without food Once Daily (Any time of Day)
Tablet	(mg15) ©Melorise	
Intravenous	Metacam© (5mg/mL) (for veterinary purpose)	

Figure 2. Elemental analysis of MLX.

2. Uses and applications of MLX

MLX has been shown to significantly reduce erythrocyte sedimentation rate (ESR), erythrocyte protein levels, and aquaporin-1 expression in patients with rheumatoid arthritis[11]. It exerts its therapeutic effects primarily through inhibition of cyclooxygenase enzymes (COX-1 and COX-2), which catalyze prostaglandin biosynthesis responsible for pain and inflammation [12]. Beyond its primary uses, MLX has recently been shown to possess several other properties, including chemopreventive, chemosuppressive, UV-sensitizing, and UV-protective effects, and it also exhibits strong antioxidant activity[13,14]. Additionally, Preclinical research (in vitro and in animal tumor models) further indicates its potential to suppress cell growth across a range of cancer types (e.g., colon, non-small cell lung cancer, osteosarcoma) at concentration ranges (10–800 μM for 24, 48 and 72 h), with specific IC_{50} values observed in certain cell lines (e.g., in PC3 cells, the IC50 decreased from 740 μM at 24 h to 515 μM at 72 h after MLX treatment)[15].

3. Pharmacokinetics

MLX exhibits an oral bioavailability of approximately 89%. However, its slow absorption is largely attributed to its limited aqueous solubility at physiological pH[16]. It demonstrates a high degree of binding to serum albumin, exceeding 99%, which can have significant implications for drug-drug interactions due as it limits free drug availability. Following oral administration, MLX reaches maximum plasma concentrations (Cmax) within 4 to 5 hours[17]. Cytochrome P450 isoenzyme CYP2C9 is the primary metabolizer, with a small contribution from CYP3A4. In (**Figure 3**) four major metabolic pathways have been identified for MLX, none of which yield active metabolites.

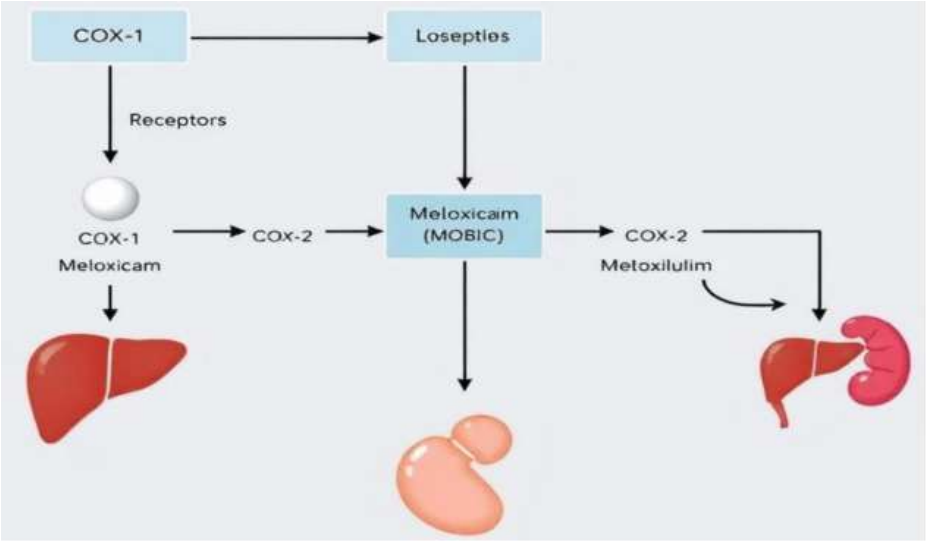

Figure 3. Metabolic pathways of MLX.

Approximately 60% of the administered dose undergoes hepatic metabolism, with CYP2C9 catalyzing the oxidation of MLX to 5'-hydroxymethylmeloxicam, an intermediate metabolite, which is subsequently

converted to the primary metabolite, 5'-carboxymeloxicam. It is important to note that CYP2C9 polymorphisms may influence the metabolic rate of MLX in certain individuals, potentially affecting drug efficacy and safety profile[18]. MLX undergoes extensive hepatic metabolism, with its metabolites excreted via renal and fecal routes. As previously mentioned, none of meloxicam's metabolites are pharmacologically active, which contributes to its predictable pharmacokinetics. Only a minimal amount of the parent compound is excreted unchanged—approximately 0.25% in urine and 1.6% in feces[19]. It exhibits a relatively long half-life of approximately 20 hours, notably exceeding that of most other NSAIDs[20]. According to FDA data, the plasma clearance rate of MLX is 7–9 mL/min. The oral LD_{50} in rats is 98 mg/kg, indicating moderate acute toxicity. Clinical signs of overdose include shallow respiration, seizures, nausea, vomiting, gastrointestinal bleeding, and melena[21].

3.1. Contraindications and precautions for MLX administration

MLX is contraindicated in specific Patients with known hypersensitivity to meloxicam or any of its excipients. Patients with known hypersensitivity to MLX or any of its excipients, gastrointestinal complications, and renal toxicity, and should be used with caution in others.

3.2. Drug interactions with MLX

MLX, similar to other (NSAIDs), can interact with several classes of medications. Concurrent administration requires careful consideration and, in some cases, is contraindicated. The following interactions have been observed:

Angiotensin-Converting Enzyme Inhibitors: NSAIDs might attenuate the ability of ACE inhibitors to lower blood pressure. This exchange may necessitate adjustments in the dosage of the antihypertensive medication.

Diuretics: MLX can attenuate the diuretic response to loop and thiazide diuretics by inhibiting renal prostaglandin synthesis. Consequently, it's advisable to carefully monitor patients' blood pressure and fluid status if they are on both medications.

Lithium: Co-administration of NSAIDs and lithium requires careful observation for signs of lithium toxicity. NSAIDs can decrease lithium clearance, leading to increased serum lithium levels. Monitoring of lithium levels is essential during concurrent use.

Methotrexate: When NSAIDs are administered alongside methotrexate, there is a heightened risk of developing methotrexate toxicity. NSAIDs can interfere with methotrexate elimination, potentially leading to elevated methotrexate levels. Caution is advised, and monitoring of methotrexate levels may be warranted.

Warfarin: The concurrent use of NSAIDs and warfarin can potentiate the risk of gastrointestinal bleeding. Both drugs have the potential to affect platelet function and/or the gastrointestinal mucosa. Careful monitoring of coagulation parameters is necessary when these agents are used together.

Cidofovir: Concurrent administration of MLX meloxicam and cidofovir is contraindicated. This is due to the heightened risk of nephrotoxicity, as both agents exert toxic effects on renal tubular cells.

4. Analytical chemistry techniques for analysis of MLX

This review summarizes various analytical methods used to determine MLX in biological matrices (such as rat muscle, human, rat, and rabbit plasma, and oral fluid) and pharmaceutical formulations (e.g., tablets, injections, and gels). (**Figure 4** and **Table 3**) illustrates the evolution of analytical techniques over the past 15 years. (**Figures 5A–C**) depict chromatographic, spectroscopic, and electrochemical methods employed in MLX analysis. The methods employed are highly sensitive, featuring low detection and quantification limits, and are accurate, showing excellent precision and recovery. Their outcomes are comparable to those obtained

using official pharmacopoeial methods. Consequently, these analytical approaches are appropriate for the regular analysis and quality assurance of MLX.

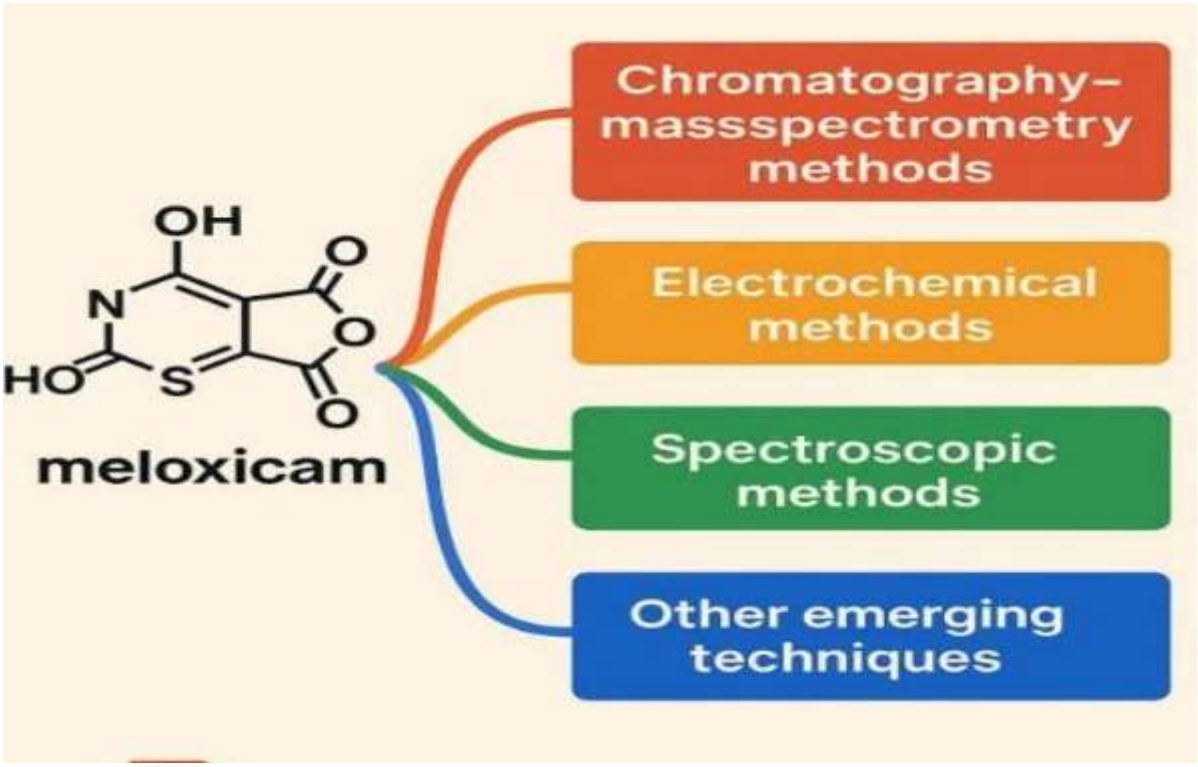

Figure 4. Analytical chemistry techniques determination of MLX.

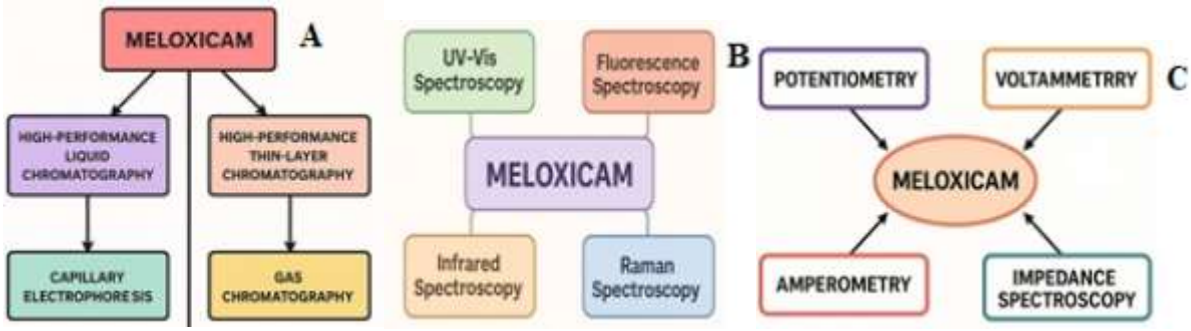

Figure 5. A, B and C Types of chromatographic, spectroscopic, and electrochemical methods used for analysis MLX.

Table 3. Analytical chemistry methods used to determination of MLX.

Method	Sample Matrix	Description	Linear Range	Limit of Detection	Ref.
TLC	Tablets and bulk drug forms	The technique involved a stationary phase of silica gel G 60F254 plates on aluminum foil. The mobile phase comprised toluene, ethyl acetate, methanol, and formic acid at a ratio of 8:2:0.5:0.5 (v/v/v/v).	75–450 ng/spot	22.5 ng/band	[23]
RP-HPLC	in human plasma and pharmaceutical formulations	MLX was separated and analyzed using an Agilent Zorbax SB C18 column and a mobile phase consisting of methanol and a 1% Diluted acetic acid. Detection was performed at 355 nm, with a gradient elution used for extraction. The total analysis time was five minutes.	20-2000 ng/mL	5 ng/mL	[24]
TLC	pharmaceutical formulations	The chromatographic separation was performed using TLC F254 plates as the stationary phase. The mobile phase comprised a volumetric ratio	50 to 2100 mg/mL	0.96 µg/ spot	[25]

Method	Sample Matrix	Description	Linear Range	Limit of Detection	Ref.
		of 2:2:1 of ethyl acetate, toluene, and butylamine, respectively. Densitometric analysis was conducted in the absorption mode at a wavelength of 297 nm.			
HPLC	rat muscle and plasma	Tissue and plasma samples underwent extraction using (Solvable^{TM} and methanol). The resulting solutions were subsequently injected onto a Hypersil ODS precolumn, previously equilibrated with 0.05 M phosphate buffer pH 3. The target compounds were backwashed with a mixture of 0.05 M phosphate buffer pH 6 and methanol (60:40, v/v). This mixture then transferred the compounds to an analytical column (YMC Pack Pro C18). Detection was performed at 360 nm.	50 to 2500 ng/g rat muscle 20 to 2500 ng/mL Plasma	15.15 ng/g in rat muscle 6 ng/mL in plasma	[26]
HPLC-UV	human plasma	Following liquid-liquid extraction using diethyl ether, MLX was chromatographically separated on a Sunfire C18 reversed-phase column (150 mm × 4.6 mm, 5 µm). The mobile phase, a pH 3.5 blend of acetonitrile and 20 mM potassium dihydrogen phosphate (40:60, v/v), was delivered at 1.2 mL/min. Detection occurred at 355 nm, yielding a meloxicam retention time of 11.6 minutes.	10–2400 ng/mL	3 ng/mL	[27]
UV spectrophotometry	tablet formulations	Measurements were performed at pH 8.5 within a 100 mM borate buffer. UV-vis absorption was recorded at a wavelength of 363 nm.	0.5 to 30 µg/mL	0.05 µg/mL	[28]
RP-HPLC	egg white and yolk	Liquid-liquid extraction was performed on egg white, and solid-phase extraction on egg yolk, resulting For separation samples, an XBridge C18 column was utilized. UV at 360 nm was used for quantification. The mobile phase, a combination of acetonitrile and diluted acetic acid, with a flow rate of 1 mL/min.	5–1500 ng/mL	1.5ng/mL	[29]
UV-spectrophotometric	residual meloxicam on manufacturing equipment surfaces	The method involves extracting residual MLX with a concentrated sodium carbonate solution and subsequently quantifying the basic form of the drug using UV spectrophotometry at a wavelength of 362 nm.	5 - 25 mg/L	1.9 mg/L	[30]
HPLC	bulk drug and commercial formulations	For reverse-phase chromatography a C18 Hi Q Sil column. A mobile phase, comprising 55% acetonitrile, 40% water, and 5% glacial acetic acid (v/v), was set to a flow rate of 1 mL/min. Detection occurred at 355 nm.	4 –20µg/ml	360 ng/ml	[31]
LC-MS/MS	oral fluid samples	Using a Shim-Pack XR-ODS 75 L × 2.0 column and a C18 precolumn, MLX was separated at 40 °C. The mobile phase, a 80:20 (v:v) blend of methanol with 10 mmol ammonium acetate, flowed at rate 0.3 mL/min. Detection was set at 625 nm.	1-10 ng/mL	0.61 ng/mL	[32]
spectrophotometric method	raw materials and in pharmaceutical formulations,	This analytical method operates on the principle that MLX creates colored ionic complexes when reacted with either copper chloride ($CuCl_2$), methylene blue (MB), or orange G (OG). These colored products exhibit maximum absorbance at 358 nm, 652 nm, and 361 nm, respectively. Under optimal conditions, linear relationships were established at pH 3.6, 5.6, and 3.6, with strong correlation coefficients of 0.9956, 0.9934, and 0.9974, at PH 3.6, 5.6, 3.6. Molar absorptivity (xl0 ^{4}) (L/mol cm) 4.36 5.04 4.70, Sandell sensitivity (µg/cm^2) 8.06 7.39 6.29, RSD% 0.213 0.134 0.266. LOQ were 1.73, 1.87, and 1.33 µg/mL, correspondingly.	1.0 to 22.1 µg/mL	0.4 µg/mL, 0.66 µg/mL and 0.8 µg/mL	[33]

Method	Sample Matrix	Description	Linear Range	Limit of Detection	Ref.
UV-spectrophotometric	pharmaceutical dosage form	Using ethanol as a solvent, MLX displayed its peak absorbance at 365 nm. Linearity according to the Beer-Lambert law was demonstrated of 2-18 µg/mL. The equation y = 0.050x - 0.005 was determined through linear regression analysis, with R^2 0.997. The method exhibited an accuracy not exceeding 2%, a specificity value of 1.28, and a mean percent recovery of 98.41% ±0.70.	2-18µg/mL		[34]
spectrophotometric and colorimetric determination	Drug	Alkaline hydrolysis of oxycamate, followed by a reaction with NBD chloride, forms the basis of these methods, which are then spectrophometrically and colorimetrically quantified at 461 nm with standard deviation percentages of 6–14% and RSD% of 4–18%	0.5 to 5 µg/mL For both method	…….	[35]
RP-HPLC	pure drug and commercially tablet form	Samples were separated on a LiChrospher RP-18 column (250 × 4.6 mm i.d., 5 µm).The mobile phase comprised 65% (v/v) 0.1 M potassium dihydrogen phosphate (pH 4.0, adjusted with phosphoric acid) and 35% (v/v) methanol. The analysis ran at a flow rate of 1.0 mL/min and a column temperature of 35 °C. Under the specified chromatographic conditions, MLX eluted at approximately 4.31 minutes and impurity B (5-methylthiazol-2-ylamine) at roughly 2.26 minutes. Data collected at 254 nm, R^2 0.999 and an LOQ of 50 µg/mL. Recoveries were determined to be within 98.57% to 101.69%.	150-450 µg/mL	5 µg/mL	[36]
Spectrophotometric	Drug and pharmaceutical preparation	The approach is based on MLX ability to reduce Fe^{+3} to Fe^{+2} These newly formed Fe^{+2} ions subsequently react with potassium ferricyanide to yield a colored complex with a peak absorbance at 708 nm. The method exhibited a high, R^2 0.9978, average recoveries ranging from 98.7% to 99.5%, with RSD% 0.56%. and LOQ 0.030 µg/mL.	0.1-11 µg/mL	0.0092 µg/mL	[37]
UPLC-MS/MS	human plasma	Quantification of MLX by Protein precipitation of samples was achieved with a 76:24:0.1 (v/v/v) mixture of water, acetonitrile, and formic acid. An Acquity HSS T3 column (2.1 × 50 mm, 1.8 µm) facilitated chromatographic separation. The mobile phase system used 10 mM ammonium formate (Phase A) and a 96:5:0.2 (v:v:v) blend of acetonitrile, water, and formic acid (Phase B). A method exhibited precision below 6.8% at LLOQ with a 98% recovery, and a total run time of 2.5 minutes.	10 - 4500 ng/mL		[38]
UV-spectrophotometry	bulk and in tablet	In 0.1 M methanol-HCl, MLX displayed an absorption maximum at 346.0 nm. The analytical technique achieved R^2 of 0.999 and an LOQ of 0.411 µg/mL.	5.0-150 µg/mL	0.13 µg/mL	[39]
UV-spectrophotometry	bulk and pharmaceutical formulation	This technique is founded on MLX interaction with sodium nitroprusside, in presence of hydroxylamine hydrochloride. The resulting colored product has an absorption maximum at 363 nm with R^2 of 0.9955. Sandell's sensitivity 0.02667 µg/cm², and the molar absorptivity 0.4849×10^{-4} L/mol cm.	4-20 µg/ mL	0.160 µg/ mL	[40]
UV-spectrophotometry	bulk and pharmaceutical formulation	The spectrophotometric technique involved MLX forming a complex with ferric chloride, which then coupled with 1,10-phenanthroline. The resultant chromophore exhibited an	10-50 µg/ mL	0.230 µg /mL	[40]

Method	Sample Matrix	Description	Linear Range	Limit of Detection	Ref.
		absorption maximum at 343 nm. This method showed good linearity, indicated by a R^2 of 0.9973 with Sandell's sensitivity 0.03195 µg/cm², and the molar absorptivity 0.4849 0.4849×10^{-4} L/moL cm.			
Direct flow injection (UV)	pharmaceutical and pure formulas	A direct technique for MLX quantification was developed, based on its coupling with diazotized procaine benzylpenicillin in an alkaline solution. The resulting colored showed peak absorbance at 492 nm. This approach yielded an LOQ of 9.08 µg/mL and a R^2 of 0.9992.	5-80 µg/mL	2.73 µg/mL	[41]
Indirect flow Injection (UV)	pure and pharmaceutical formulations	An indirect method was devised, predicated on a charge transfer reaction.Here, the alkaline hydrolytic product of MLX operated as an n-donor, reacting with metol (p-methylaminophenol sulfate) as a π-acceptor, with sodium periodate acting as the oxidant, The colored products exhibited absorption at 656 nm with R^2 0.9993 and LOQ 17.52 µg/mL	15-225 µg/mL	5.26 µg/mL	[41]
3 D-UV	bulk and tablets	Using third-order derivative spectrophotometric method depending a peak-tozero measurement technique for the determination of MLX in tablet formulations at 341 nm with LOQ 0.75 µg/mL and recovery percentage was between 97.50% and 98.12%.	1.0-14 µg/mL	0.22 µg/mL	[42]
UV-spectrophotometry	pure form and pharmaceutical	The technique involves diazotizing the (NH_2) group in 4-nitroaniline with $NaNO_2$ followed by a reaction with MLX to produce a stable and colored complex in a basic medium. This complex exhibits a maximum absorbance at 514 nm. molar absorptivity was 1.5989×10^4 L/ mol cm with RSD was found to be less than 1.55%.	2- 25 µg/mL	0.2019 µg/mL	[43]
batch and flow-injection	pure form and pharmaceutical	The batch method is founded a green complex formed between the drug and Fe(III) in a methanolic. This complex, designated as [2MLX/Fe(III)], exhibits its greatest absorbance at 570 nm. For the second method, flow-injection spectrophotometry is employed to measure the drug's absorbance at 362 nm (0.1 M) NaOH. This approach demonstrated strong linearity, with a R^2 of 0.9998	2.0–200 and 5.00–250 µg/mL (batch) 0.5–20 µg/mL (flow injection)	0.47 - 0.72 µg/mL (batch) 0.04 µg/mL (flow-injection)	[44]
Spectrophotometric	pure and tablet	Method I utilizes the simultaneous equation approach, employing the absorbance maximum of MLX at 268.8 nm. Method II is based on Q-value determination, with 308 nm (Isobestic point) with a R^2 of 0.9975, LOQ 0.3805 and 0.2449 µg/mL for Method I and II.	5-30 µg/mL	0.1255 µg/mL (method I) And 0.0808 µg/mL (method II)	[45]
flow injection analysis	pharmaceutical preparations	The method involves the oxidation of MLX by NBS in an acidic environment. Following this, the remaining NBS interacts with chloranilic acid (CAA), resulting in a loss of CAA's purple coloration. The method exhibited R^2 0.9940, RSD % 1.2, LOQ 20 mg/L. The colored products resulting from the initial oxidation reaction exhibited an absorption maximum at 530 nm.	10 – 160 µg/mL	6 mg/ L	[46]
Voltammetric	pharmaceutical formulations	For the direct quantification of MLX, two new voltammetric techniques, square wave voltammetry (SWV) and differential pulse voltammetry (DPV), were introduced. Anodic peaks were detected in a pH 4.85 buffer solution when a glassy carbon electrode (GCE) was	10-90 µg/mL	0.50 µg/mL	[47]

Method	Sample Matrix	Description	Linear Range	Limit of Detection	Ref.
		employed. Both methods exhibited a LOQ of 1.50 µg/mL. RSD were 2.72% and 3.06% for the SWV and DPV methods, respectively.			
Electrochemical oxidation	pharmaceutical formulations	The electrochemical oxidation of MLX was studied for the first time using a (BDDE) generated two irreversible anodic current peaks were detected with a saturated silver-silver chloride reference electrode. LOQ of 1.9×10^{-7} mol/ L, LDR (1 2.5×10^{-7} - 8.5×10^{-5}mol/ L) and RSD 0.3 %	2.5×10^{-7} and 8.5×10^{-5} mol/L	5.9×10 to 8 mol/ L	[48]
Polarographic	tablets and spiked plasma.	This study examined of MLX voltammetric properties through DC polarography, DPP, and CV. The best DPP results occurred in an acetate buffer at pH 4.88. Using a static mercury drop electrode, peak currents were detected at -1.49 V against Ag/AgCl. The method established an LOQ of 0.38 µg/mL, and coefficient of variance of 2.35% at the LOQ (n=6).	0.38 to 15 µg/ mL	0.02 µg/ mL	[49]
Capillary zone electrophoresis	transdermal therapeutic systems	An optimized CZE method was developed using a 50 mM borax background electrolyte (pH 9.3). The procedure involved an applied voltage of +25 kV, a 5-second hydrodynamic injection at 50 mbar, and a temperature of 40°C. Analysis times were under four minutes, providing a resolution of 7.79 at 335 nm. The method's performance metrics included LOQ of 54.55 µg mL^{-1} and an R^2 of 0.9983.	……	16.05 µg /mL	[50]
capillary zone electrophoresis	pharmaceutical tablets	The separation method utilized a 100 mM borate buffer (pH 8.5), incorporating 5% methanol. Key parameters included a capillary temperature of 25 °C, an applied voltage of 20 kV, and a 3-second hydrodynamic injection. Detection occurred at 205 nm. The technique's precision was notable, showing an RSD of 0.66%	0.5 to 150 µg/ mL	0.3 µg /mL	[51]
UV Spectroscopy	Drug and medicinal preparations	A simple and accurate development of a method for MLX estimation in bulk drug and tablet formulations at 269 nm, with 0.1 M NaOH as the solvent, with R^2 0.9995. LOQ of 108.07 ng/mL, a low %RSD 0.0130, Sandell's sensitivity was determined to be 0.4756 µg/mL, and molar absorptivity was 2.1066 X 10^4 g/L mole.	5 – 30 µg/mL	37.8 ng/mL	[52]
COLORIMETRY	Drug and medicinal preparations	This spectrophotometric technique involved the use of a solvent consisted of a 0.1 M NaOH solution, with the inclusion of 5% ferric chloride. for chromogen development. The green chromogen formed had its highest absorbance at 476 nm and a R^2 0.9986, LOQ of 936.02 ng/mL, RSD 0.0068%. Additionally, the Sandell's sensitivity was 2.752 µg/mL, and the molar absorptivity was 3.633 x 10^3 L/ mol/ cm.	50 – 250 µg/mL	327.60 ng/mL	[52]
HYDROTROPIC	Drug and medicinal preparations	The addition of a 10% trisodium citrate solution, acting as a hydrotropic agent, led to improved solubility. MLX concentrations were subsequently measured spectrophotometrically at 269 nm, yielding a R^2 of 0.9987 LOQ was 108.1 ng/mL, RSD 0.0294%, Sandell's sensitivity 0.5745 µg/mL.molar absorptivity 2.5648 x 10^4 L/ mol cm.	5 – 30 µg/mL	37.84 ng/mL	[52]
RP-HPLC	rabbit's plasma	Isocratic elution was carried out on a Kromasil W (C18 column 250 × 4.60 mm, 5 µm particle size). The mobile phase comprised methanol-water (8:2, v/v), with pH adjusted to 3.0 using orthophosphoric acid. Methanol and diethyl	10 to 50 ng/mL	4 ng/mL	[53]

Method	Sample Matrix	Description	Linear Range	Limit of Detection	Ref.
		ether were used for protein precipitation at 228 nm. Analysis maintained a flow rate of 0.8 mL/min at ambient temperature, under an average operating pressure of 1400 psig. The analyte, MLX, displayed a retention time of 6.960 min, and a resolution of 3.18. The method demonstrated a strong linear relationship, evidenced by R^2 0.9972.			
RP – UPLC	pure and pharmaceutical formulations.	The developed analytical technique provided acceptable separation of MLX, which exhibited a retention time of 3.687 minutes. Based on the regression analysis, LOQ was determined to be 0.06 ppm, with a R^2 of 0.9998.	1.5-9 ppm	0.0 I 8 ppm	[54]
HPLC	Injections	A LiChrospher 100, RP-18 (5 µm) column was employed for separation. The mobile phase consisted of acetonitrile and ultrapure water in a 60:40 ratio, achieving R^2 0.999. Key parameters for the analysis included a controlled temperature of 25 °C, 10 µL of sample was injected into the system, which ran at a flow rate of 1.5 mL/min, with detection at 360 nm, and run time spanned 10 minutes.	0.05-0.30 mg/mL	……	[55]
HPLC	Tablet	The procedure parameters were set as follows: a flow rate of 0.8 mL/min, variable column temperature, 290 nm detection wavelength. A 10 µL injection volume was employed. The mobile phase was a 30:70 (v/v) blend of methanol and an aqueous solution (0.6% trifluoroacetic acid, pH 2.6) LOQ 1.0 µg/mL and a RSD % 3.9.	1.0 to 50 µg/mL	0.25 µg/mL	[56]
UV spectrophotometry	MLX niosomal hydrogel	Niosomes were prepared using the thin-film hydration method, incorporating cholesterol along with various nonionic surfactants. A specific niosomal formulation, consisting of Span 60, Tween 80, and cholesterol in a 6:1:0.6 molar ratio, With (λmax) of 362 nm and LOQ of 1.302 µg/mL, in vitro release experiments demonstrated a maximum drug release of 46.83% within 24 hours.	1–30 µg/mL	0.430 µg/mL	[57]
HPLC	MLX loaded PEGylated nanocapsules(M-PEGNC)	Interfacial polymer deposition was the chosen method for synthesizing PEGylated nanocapsules from MLX. Following synthesis, their characteristics, including particle size, polydispersity index, zeta potential, pH, and encapsulation effectiveness, were determined. The associated quantification technique showed an LOQ of 1.78 µg/mL and an RSD% of 1.35%.	1.0-40.0 µg/mL	0.59 µg/mL	[58]

Table 3. (*Continued*)

5. Future projects

This review has a range of analytical techniques employed to measure MLX in pharmaceutical formulations and biological matrices. The diverse methodologies discussed, including spectrophotometric, chromatographic (HPLC, UPLC-MS/MS, LC-MS), and electrochemical methods, demonstrate the range of options available for MLX analysis. Each technique offers unique advantages and disadvantages concerning sensitivity, selectivity, cost-effectiveness, and sample preparation requirements. Consequently, the optimal method selection depends on the specific analytical objectives and the complexity of the sample matrix. While spectrophotometric methods remain suitable for routine analyses due to their simplicity and cost-effectiveness, HPLC is frequently preferred for its superior sensitivity, and ability to resolve MLX from other components in complex matrices. Overall, the future of MLX measurement will likely be driven by the need for more

sensitive, selective, rapid and efficient methods. These techniques demonstrate excellent analytical performance, with low limits of detection (LOD), high accuracy, and good precision and recovery. Results obtained are comparable to those of official pharmacopoeial methods, confirming their applicability in routine quality control and pharmacokinetic studies of MLX. The development of new analytical techniques such as mass spectrometry and immunoassays, as well as the use of biosensors, may lead to major advances in this field in the future.

Conflict of interest

The authors declare no conflict of interest.

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