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A Review of HPLC and UPLC Methods for Quantifying Domperidone in Plasma and Serum Matrices in Pharmacokinetic Research

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ABSTRACT

Domperidone is recently being developed into various better formulations to improve its bioavailability. Meanwhile, the usage of domperidone together with certain other drugs may cause the interaction between the drugs. Therefore, a pharmacokinetic study is needed to provide bioequivalence data for the new formulations and to evaluate clinical interaction evidence. Plasma or serum is commonly used as a biological sample in pharmacokinetic evaluation. It is critical to have a simple, sensitive, and valid method for determining domperidone in biological matrices. Liquid chromatography offers excellent performance in quantifying the drug in plasma. This review describes the application of high-performance liquid chromatography (HPLC) and ultra-performance liquid chromatography (UPLC) coupled with different detectors to quantify domperidone in plasma or serum matrices. Several extraction methods of sample preparation are also highlighted.

1. Introduction

Domperidone is a weak base (pKa=7,89), low molecular weight (MW= 425,9), practically insoluble in water, and the lipophilicity value of the drug (Log P) is 3,90 [1,2]. It is a dopamine antagonist widely prescribed to treat nausea and vomiting [3]. Domperidone has been reported could ameliorate functional dyspepsia symptoms and infant nausea and vomiting [4]. The drug has also been used for post-chemotherapy vomiting and gastroparesis. Domperidone is typically administered at a dose of 10 mg up to three times per day [5,6].

Domperidone plasma levels reach their peak between 10 and 30 minutes after intramuscular or oral administration. Meanwhile, rectal administration (suppositories) is commonly within 1 to 2 h. Maximum plasma concentrations of domperidone after a single dose vary depending on the dosage form. The reported maximum plasma concentration of the intramuscular route is approximately 40 ng/mL, oral (tablet) is 23 ng/mL, oral (drops) is 102 ng/mL, and rectal (suppository) is 20 ng/mL. Domperidone has a 90% bioavailability after intramuscular administration, but only a 13-17 % oral bioavailability [7,8]. This low oral bioavailability is due to its poor solubility, extensive first-pass effect, and efflux by small intestine transporters [9,10]. Domperidone is an active substrate of Cytochrome P4503A4 (CYP3A4) and the active efflux transporter P-glycoprotein (P-gp), which causes extensive metabolism [11,12]. After oral administration, the elimination half-life in healthy participants is about 7.5 h, and approximately 66% of the drug is detected in the feces [7].

Recently, domperidone has been developed into various better formulations with advanced technology. This is conducted to improve its solubility, which leads to an increase in its bioavailability- Furthermore, the drug has been incorporated into novel drug delivery systems to achieve more efficient and targeted delivery [2,10,13–18]. Thus, *in vivo* tests, such as pharmacokinetics, are necessary to evaluate and provide the bioavailability and bioequivalence data for those formulae. On the clinical side, domperidone is widely used to prevent gastrointestinal symptoms, either caused by common disorders or induced by other drugs such as cytotoxic drugs. The use of domperidone concomitant with another drug, such as multidrug resistance protein 1 (MDR 1) inhibitors and/or CYP3A substrates or inhibitors, could have an influence on systemic pharmacokinetics. Thus, the clinical evidence is crucial to prove and describe the domperidone and other drug interactions to ensure the appropriateness of domperidone usage in clinical practice [19–21]. Therefore, pharmacokinetic studies should also be conducted for this reason.

In pharmacokinetic studies, the biological sample often used is plasma or serum. Analysts face numerous challenges when examining drugs in those biological matrices. The selectivity of the method, as well as its sensitivity and elimination of matrix effects, could be major limitations [22,23]. In addition, the concentration of domperidone is very low that can be detected in plasma for *in vivo* tests. Thus, the sample preparation and the sensitivity of the instrument are critical [24].

Plasma is composed of complex components that could interfere with the quantitative analysis of the drug [25]. Serum is the clear component of blood that remains after the removal of cells, platelets, and clotting factors. It differs from plasma, which is the supernatant separated from blood with the use of an anticoagulant [26]. Providing reliable data in plasma or serum matrices for pharmacokinetics studies, wether in animal or human tests, requires a sensitive, selective, rapid, and simple method. Liquid chromatography is a method that is widely used in all analytical technique laboratories for bioanalysis.

Since plasma and serum are the matrix of interest in this article and the most often and popular instruments used for their analysis are high-performance liquid chromatography (HPLC) and ultra-performance liquid chromatography (UPLC), we have summarized the utilization of both techniques, including sample preparation and extraction methods for analyzing domperidone in both biological matrices. This review also discusses the advantages and disadvantages of the implementation of these methods during the analysis.

2. Methods

Several databases, such as PubMed, Scopus, ScienceDirect, and Google Scholar, were used as sources for this review. The original research article type related to the analysis techniques for quantifying domperidone in plasma matrices that use HPLC and UPLC was identified and selected from those databases. The keywords used were domperidone+liquid chromatography+plasma+serum for searching articles in databases. The inclusion criteria for the studies in the review article require the use of a validated HPLC or UPLC method for the quantification of domperidone. The biological matrix consists of human or animal plasma/serum, and the studies include complete analytical performance parameters and are written in English. Meanwhile, the exclusion criteria specified that studies lacking sufficient analytical validation data, those that did not apply the method in pharmacokinetic contexts, as well as review articles, editorials, and conference abstracts, were not included. A total of 16 articles were selected for the review.

3. Results and Discussion

3.1 Plasma Sample Preparation

Sample preparation is an important point in the bioanalytical process [27]. Before being injected into the system, a biological sample, such as plasma, must go through sample preparation steps. Pre-treatment of plasma samples aims to remove the proteins and other potential interferences. This step was essential not only to eliminate the matrix effect but also to prevent the chromatographic column from damage [28,29]. Several techniques in sample preparation generally involve liquid-liquid extraction (LLE), solid-phase extraction (SPE), and protein precipitation [25,30.]

The LLE technique uses two or more immiscible solvents that are not in equilibrium. Meanwhile, SPE separates the analyte from the complex mixture using a liquid and solid phase. SPE often required more sequential steps and complicated procedures [31,32]. The simplest way of sample extraction might be plasma protein precipitation, where its supernatant can be analyzed directly into the system, while SPE and LLE need a further procedure to obtain good recovery before being injected [25,33]. The protein precipitation technique involves the addition of precipitating solvents such as methanol, ethanol, acetonitrile, or acetone [34].

In a bioanalysis assay, an internal standard is added at the earliest step and processed along with the sample. The internal standard is chosen based on the similarity of behavior to the analyte [35]. Considering both chemical similarity, as well as instrumental detection factors [36]. In the process of running samples, both the analyte and internal standard are analyzed simultaneously. The use of an internal standard is considered to help compensate for any variation that may occur during sample preparation and analysis [37,38].

Regarding the analysis of domperidone in the plasma and serum matrix, several extraction methods have been reported for separating domperidone from the sample matrix, which are briefly described in this article. Internal standards generally used to analyze domperidone in the matrix using liquid chromatography, are presented in Table 1.

3.2 HPLC and UPLC

Most analysis of domperidone in plasma matrix is performed by high-performance liquid chromatography (HPLC) and ultra-performance liquid chromatography (UPLC). The bioanalysis process using this instruments can not be separated from the optimization on the mobile phase and detector during the method development.

A good separation, proper retention time, and sharp peaks can be provided by optimizing the mobile phase [39]. The mobile phase in LC extensively consists of water, methanol, and acetonitrile. The use of Buffer and the addition of an additive to solvent is a common practice in the preparation of the mobile phase to achieve a specific purpose such as modifying pH, ion-pairing, or ionic strength. These factors affect not only the retention time of the analyte but also its ionization in mass-spectrometric (MS) detectors [40]. The pH selection of the mobile phase becomes

Table 1. HPLC and UPLC methods used for the quantification of domperidone in biological matrix

Matrices	Instrument	Column	Chromatographic Condition	Internal Standard	Reference
Human Plasma	HPLC UV-Vis	C_{18} symmetry column (150 mm x 4.6 mm, 5 μm)	Mobile phase: Phosphate buffer (50.0 mM, pH 3.0)- acetonitrile (80:20, v/v) Flow rate: 2.0 mL/min Detection: 240 nm	Celiprolol	47
Human Plasma	HPLC-UV	Luna Phenomenex® C18 (250 mm × 4.6 mm i.d; 5 μm)	Mobile phase: mixture of phosphate buffer 0.02 M: acetonitrile (70:30, v/v) Flow rate: 1.0 mL/min Detection: 285 nm	Propranolol HCl	48,49
Human Plasma	HPLC-Fluorescence	XBridge™C18 column (150 mm × 4.6 mm, 5μm)	Mobile phase: Acetonitrile-10 mM ammonium acetate buffer (36:64, v/v), pH 9.4 Flow rate: 1.0 mL/min Column temperature: 40°C Detection: Fluorescence detector at excitation 282 nm and emission 328 nm	Propranolol	21
Human Serum	HPLC-Fluorescence	ACE 5C18 (250 mm × 4.6 mm I.D.)	Mobile phase: Methanol- 0.02 M monobasic potassium phosphate (pH = 3.5) (49:61) Flow rate: l mL/min, Detection: Fluorescence detector at excitation 282 nm and emission 328 nm	Propranolol	50
Dog Plasma	HPLC-MS	Narrow Bore C18 column (150 mm x 2.1 mm, 5 μm)	Mobile phase: methanol-10 mM ammonium acetate (68:32, v/v) Flow rate: 0.2 mL/min, Column temperature: 30°C Detection: Selected ion-monitoring (SIM) mode; ESI in positive ion mode	Diazepam	51
Human Plasma	HPLC-UV	Hypersil BDS C8 column (150 mm × 4.6 mm, 5 μm)	Mobile phase: Water (pH 3.0)- acetonitrile (65:35 v/v) Flow rate: 1.5 mL/min Column temperature: 40°C Detection: 210 nm	Tenofavir	52

Table 1, continued

Rat Plasma	HPLC-UV	C_{18} Sunfire™ (5 µm, 250 mm × 4.6 mm)	Mobile phase: Acetonitrile-methanol (30:70) Flow rate: 1 mL/min Column temperature: 30 ± 1 °C Detection: 270 nm	Irbesartan	53
Human serum	HPLC-UV	C18 column, (4.6 ×250 mm; 5 mm bead size)	Mobile phase: Acetonitrile: 0.01 M sodium salt of heptane sulphonic acid (58:42% v/v); pH = 3± 1 Flow rate: 1 mL/min Detection: 230 nm	Pyridoxine	54
Human Plasma	HPLC MS/MS	C8 column, (50 mm x 3 mm, 3 µm)	Mobile phase: Water-methanol (2:98, v/v) containing 0.5% formic acid Flow rate: 1 mL/min Column temperature : 23°C Detection: ESI with multiple reaction monitoring (MRM) mode; ESI in positive ionization mode	Pantoprazole	37
Human Plasma	HPLC-MS/ MS	C8 column (50 mm × 3 mm, 3 µm)	Mobile phase: Water: methanol (2: 98, v/v) containing 0.5% formic acid Flow rate: 1 mL/min Column temperature: 23°C Detection: a triple quadrupole mass spectrometer with ESI source (positive mode)	NA	55
Human Plasma	HPLC-MS/ MS	ACE C_{18} (50 mm x 4.6 mm, 3 µm)	Mobile phase : Formic acid in water (0.1%)-acetonitrile (25:75, v/v) Flow rate: 0.5 mL/min Detection: MRM mode; ESI in positive mode	Atorvastatin	56
Human Plasma	HPLC-MS/ MS	Phenomenex Luna C_8(2) (150 mm x 2 mm, 5 µm)	Mobile phase: Acetonitrile-0.02% formic acid (300:700, v/v) Flow rate: 0.2 mL/min Detection: Applied Biosystems Sciex API 2000 mass spectrometer set at unit resolution in the MRM mode	Melperone	57

Table 1, continued

Human Plasma	HPLC-MS/MS	Reversed Phase Column	Mobile phase: Methanol-water-ammonia solution(80:20:0.2, v/v) Detection: MRM on a Q-trap™ LC/MS/MS system	Tramadol	58
Human Plasma	HPLC MS/MS	C18 reversed phase column	Mobile phase: acetonitrile-glacial acetic acid (0.3 %) (40:60, v/v) Detection: MRM mode; ESI in positive mode	Paracetamol	59
Human Plasma	UPLC-MS/MS	Acquity BEH C_{18} column (50 mm x 2.1 mm, 1.7 μm)	Mobile phase: Acetonitrile- water containing 1% formic acid in gradient elution Flow rate: 0.45 mL/min Detector: a triple quadrupole tandem mass spectrometer equipped with an ESI interface (positive mode)	Oxcarbazepine	60
Human Plasma	UPLC-MS/MS	Acquity UPLC™ BEH C_{18} column (50 mm x 2.1 mm, 1.7 μm)	Mobile phase: Methanol–water containing 10 mmol/L ammonium acetate and 0.5% (v/v) formic acid (60:40, v/v) Detector: a triple quadrupole tandem mass spectrometer equipped with an ESI interface (positive mode)	Diphenhydramin	61
Human Plasma	UPLC MS/MS	Xterra MS C18 Column (2.1 × 150 mm, 5.0 μm)	Mobile phase: A gradient program combining 0.1% formic acid and acetontrile Flow rate: 0.30 mL/min	Mosapride	62

*Electrospray ionization (ESI)
*Not Available (NA)

an important point that affects the analyte retention with acidic-basic properties, and also influences the analyte interactions with the stationary and mobile phases [40,41]. Ionizable functions, such as amino or carboxylic groups, are present in most pharmaceutical and biological compounds [42].

Domperidone has a pKa value of 7,9 [43]. If the mobile phase pH used is lower than pKa, domperidone will be ionized, primarily carrying a positively charge and showing a shorter retention time in reversed-phase liquid chromatography.

3.2.1 Detection

LC-coupled with a particular detector gives a different performance of the analysis. It can affect the

sensitivity and selectivity. Various detectors can be coupled with the LC system either in single or multiple detections. The single detection commonly used is UV, photodiode array (PDA) detector, fluorescence detector, or mass spectrometry (MS); meanwhile, the multiples such as LC-MS-MS and LC-UV-Visible-MS [39,44,45]. LC-UV detectors are the most feasible method and are less complicated compared to using other detectors. Meanwhile, a PDA detector, a type of UV detector, can detect the entire spectrum in the range of UV to visible wavelengths. Fluorescence detectors have 10-1000 times greater sensitivity than UV or PDA detectors. MS detectors usually involve two or more MS detectors (tandem MS/MS) to obtain better results analysis of the sample, owing to high selectivity and sensitivity [39,46]. The liquid chromatographic conditions for the quantification of domperidone are compiled in Table 1.

3.2.2 High-performance liquid chromatography (HPLC)

HPLC has been a popular and powerful technique to identify and quantify a compound from complex mixtures such as chemical and biological samples (e.g., plasma). A column in reversed -phase HPLC is commonly packed with octadecyl (C18) silica (3–5 μm particle size) [63].

Determination of domperidone in plasma or serum matrix, using an HPLC system, has been reported by several research groups. Ali et al. (2014) used the HPLC-UV method for determining domperidone in plasma. For the drug extraction from the plasma the solid-phase extraction (SPE) method was employed. The detection limits for domperidone and celiprolol (used as the internal standard) were 1.0 and 1.2 μg/mL, respectively [47]. This indicatesthat the detection limit is relatively high, which may limit its application in low-concentration samples.

Pawestri et al. (2021) developed an HPLC-UV method to determine domperidone in plasma matrix from human plasma. Domperidone was extracted from the sample by using acetonitrile as a deproteinating agent. The method linearity was 0.998 within the concentration range of 15–200 ng/ml. The separation time of the proposed method was less than 10 min. The lower limit of quantification (LLOQ) was 15 ng/mL [48,49]. The developed method makes it efficient for routine use.

Salehi et al. (2016) established a technique for the selective quantification of domperidone in biological samples by utilizing molecularly imprinted polymers (MIPs) as a sample purification method alongside an HPLC-fluorescence detector. The findings indicated a remarkable affinity for domperidone in biological fluids. The analytical procedure exhibited linearity r^2 = 0.9977 in the range of 5–80 ng/mL, The limit of detection (LOD) and limit of quantification (LOQ) for domperidone were 0.0279 and 0.092 ng/mL, respectively. The method's simplicity and appropriate validation parameters make it an extremely valuable bioequivalence technique in regard to sensitivity and selectivity for analyzing domperidone in human serum[50].

Vij et al. (2023) created a method for the simultaneous measurement of cinnarizine (CIN) and domperidone (DOM) in rat plasma. The compounds (CIN and DOM), along with the internal standard (IS), were extracted from plasma samples using a protein precipitation technique with a combination of methanol and acetonitrile (1:1 v/v). DOM, CIN, and IS were detected at 3.2, 4.5, and 6.1 minutes, respectively, with a total analysis time of 10 minutes. The lower limit of quantification (LLOQ) was determined to be 5 ng/mL for both CIN and DOM. The suggested RP-HPLC method exhibited linearity within the range of 5–200 ng/mL for CIN and DOM with r^2 equal to 0.999 and 0.998 respectively. The method's recovery exceeded 95%, and the relative uncertainty was below 2%, demonstrating that the proposed bioanalytical method was both accurate and precise. The limit of detection was found to be 1.1 ng/mL for CIN and 1.7 ng/mL for DOM [53]. These methods are fast and show fast and high sensitivity and recovery.

Several researchers employed more advanced detection systems. Li et al. (2009) determined domperidone simultaneously with omeprazole in dog plasma with diazepam as IS. The drug was extracted from dog plasma by using sodium hydroxide and diethyl ether. The drug's detection was measured by a mass spectrometer equipped with electrospray ionization (ESI) in selected ion monitoring mode. Target

ions were at m/z 426 for domperidone, while m/z 346 for omeprazole. The ESI used was in a positive mode due to the presence of an amide group in the structure of domperidone and omeprazole. The separation time of this method is less than 7 min. Good linearity was achieved in the range of domperidone concentration of 1-200 ng/mL, while the LLOQ of domperidone was 1 ng/mL. This method fulfilled the requirement for bioanalytical studies [51]. Mohi et al. (2018) studied the bioavailability of micronized tablets compared to conventional tablets of domperidone using human plasma from healthy Indian male volunteers. The detection was achieved using ESI in positive mode and with multiple reaction monitoring (MRM) mode. The process analysis required 5 min. Domperidone peak appeared at 1.67 min, while the internal standard was 2.03 min. LLOQ was observed at 3.33 ng/mL, and the linearity range was within 3.33-500 ng/mL [55]. Bayyari et al. (2015) also developed and validated the reversed-phase HPLC-MS/MS method in the positive mode of ESI to measure domperidone in human plasma. The linearity of the method was in the range of 0.101-30.300 ng/mL. Domperidone was extracted from plasma using tert-butylmethyl ether, and the samples were evaporated at room temperature under a stream of nitrogen. The detection of domperidone using MRM mode and monitored at m/z 426.2 → 175.1 and m/z 559.5 → 440.4 for the internal standard [56]. This method achieved higher sensitivity, making it suitable for trace analysis in human plasma.

Some studies also addressed multi-analyte detection. Sher et al. (2014) and Khan et al. (2016) developed methods for the simultaneous determination of domperidone with other drugs. Sher et al. (2014) performed a simultaneous analysis of cetirizine HCl (CZ), chlorphenamine maleate (CPM), loratadine (LTD), domperidone (DP), buclizine (BZ), and meclizine (MZ) in pharmaceutical formulations and human serum, using pyridoxine (PYD) as the internal standard. The precision measurements for both intraday and interday showed coefficients of variation that were consistently below one. The calibration curve was evaluated within a concentration range of 10-2150 ng/mL, yielding a correlation coefficient greater than 0.9990 in all instances. The average absolute and relative recoveries were determined to lie between 98% and 102%. A maximum of six antihistamines were successfully separated in a single chromatogram with adequate resolution. The suggested HPLC method demonstrates practical applications for pharmaceutical tablet formulations and pharmacokinetic studies [54].

Khan et al. (2016) developed and validated an RP-HPLC/UV method to determine domperidone and itopride simultaneously in pharmaceutical samples and human plasma. A precipitation technique using acetonitrile for deproteination was applied for drug extraction from human plasma. The developed method was quite linear in the range of 20–600 ng/ml. The LLOD and LLOQ for domperidone were 5 and 10 ng/ml, while for itopride, they were 12 and 15 ng/ml, respectively. Both analytes had a retention time below 15 min. The in vivo analysis of fast-dispersible tablets of domperidone in healthy human volunteers using the proposed method was successfully implemented [52].

Bose et al. (2009) also reported an HPLC tandem mass spectrometry method to determine domperidone and itopride hydrochloride simultaneously in human plasma. Liquid-liquid extraction using ethyl acetate and saturated borax solution (90:10) was conducted in sample preparation. The detection using the ESI source was in the positive mode, as the intensity of ion peaks was higher. MRM mode was selected where ion transitions were performed in m/z 359.1–72.3 and 426.0–147.2 to measure itopride hydrochloride and domperidone, respectively. The linearity exhibited in the range of 3.33–500 ng/mL for domperidone. The run time analysis only required 3 min [65]. These developed methods highlight the potential of HPLC for pharmacokinetic studies involving drug combinations.

Kobylińska et al. (2000) examined domperidone in human plasma for pharmacokinetic studies using a reverse-phase HPLC-fluorescence detector. The SPE method using nitrile SPE cartridges was used to isolate domperidone. The mobile phase is composed of methanol-triethylamine-acetic acid. The analysis was run by fluorometric detection after post-column photoderivatization. LLOQ of this method was 1 ng/mL [64]. Meanwhile, in clinical stud-

ies, Yoshizato et al. (2014) also proposed and validated a reversed-phase HPLC-fluorescence detector method to determine domperidone concentration in a pharmacokinetic interaction study in presence of itraconazole. Plasma samples were extracted by the SPE technique with Bond Elut®C18. From this method, domperidone and internal standard were found at 8.3 and 11.2 min, respectively. A good linearity (r>0.999) was achieved in 1-100 ng/mL concentration of domperidone. The LLOQ of the method was 1.0 ng/mL. The method was was successfully used for the determination of domperidone in clinical application [21].

Most analytical studies aim to balance between sensitivity, complexity, and throughput in their methodologies. Utilization of SPE and an HPLC-fluorescence detector provide good sensitivity for quantifying domperidone in plasma. Methods based on Molecular imprinted polymers (MIP) and Mass Spectrometry (MS) offer superior sensitivity, but they have higher costs and increased operational complexity. On the other hand, UV-based methods utilize simpler extraction techniques, allowing for faster analysis with moderate sensitivity. Overall, HPLC remains a versatile platform for analyzing domperidone, with the choice of method depending on the required sensitivity, the type of sample, and the available instrumentation.

3.2.3 Ultra-performance Liquid Chromatography (UPLC)

Ultra Performance Liquid Chromatography (UPLC), known as an advanced liquid chromatography technique, provides a shorter analysis time and low consumption of solvents as a mobile phase compared to HPLC systems. Process separation in UPLC is performed at very high pressures up to 100 MPa due to the small particle size (< 2 μm) in the UPLC column. It also indicates that the UPLC system offers a higher separation efficiency than the HPLC system, as the diffusion path between the stationary phase and the analytes is shorter [66,67].

Qiu et al. (2014) developed and validated a UPLC–MS/MS method for determining domperidone in human plasma. The procedure employed one-step precipitation using methanol and the analysis time was 1.5 min. Good linearity was observed in the concentration range of domperidone within 0.25–100.0 ng/mL. The method was applicable for a pharmacokinetic study in healthy volunteers after administering domperidone orally, demonstrating its efficiency and clinical relevance. [60].

Wang et al. (2012) have reported using the UPLC-MS/MS method for the validation of domperidone in human plasma. One liquid-liquid extraction was conducted with a mixture of diethyl ether-dichloromethane (3:2, v/v). The validation results showed good linearity in the range of 0.030-31.5 ng/mL. Besides, the LLOQ value was 0.030 ng/mL, indicating the method is very sensitive. The running time for analysis was just 2.1 min. The method was successfully applied to the pharmacokinetic study of healthy humans after being administered with a domperidone orally disintegrating tablet [61].

Xu et al. (2008) also reported a UPLC MS/MS method for determining domperidone in human plasma. Protein precipitation using methanol (containing 0.1% formic acid) produced clean extracts, so interferences from the matrix were absent at retention times of domperidone and internal standard. LLOQ was 0.2 ng/mL and the method satisfied the linearity of domperidone in the range of 0.2–60.0 ng/mL. The analysis needed about 4.0 min of run time, and the sample volume was 0.1 ml. This method was successfully applied to a bioequivalence study [62], indicating suitability for the utility of UPLC for clinical trials.

Compared to HPLC, UPLC methods provide significantly better sensitivity, lower limits of quantification (LLOQ), and shorter analysis times, often needing less than 2 to 4 minutes. This makes UPLC highly suitable for high-throughput bioanalytical applications. However, the need for specialized equipment and the capability to handle high pressure may pose a limitation for some laboratories.

3.3 Advantages and disadvantages of HPLC and UPLC Methods

Among the above mentioned studies the shortest run time (1.5 min), was acieved by employing LC-MS/MS

method, using a simple one-step protein precipitation procedure for sample preparation and UPLC-MS/MS instrumentation [60].

For simultaneously quantification of multiple drugs, HPLC-MS/MS analysis can provide greater resolution and shorter run time, as demonstrated by Bose et al. who were able to obtain a total run time of 3 min, which is extremely quick for a multi-drug detection approach [65]. The mobile phase were acidified using formic acid and ESI in positive ion mode was used as the most often employred method to analyze domperidone in LC-MS.

In other cases, domperidone was analyzed using HPLC–UV methods [47,52]. One study employed the SPE technique, while another used the protein precipitation technique to extract the drug from plasma. However, adjustments of the chromatographic conditions in the protein precipitation method resulted in a better sensitivity (LLOQ = 5 ng/mL) compared to the SPE method (detection limit 1.0 μg/mL). In addition, the SPE technique is generally more complicated and needs more time for sample preparation than protein precipitation. Such issues should be considered to achieve good sensitivity in HPLC–UV analyses of domperidone.

The use of HPLC-fluorescence to determine domperidone [21,64]. offers a better LLOQ than a UV detection. However, this approach requires complicated sample pre-purification to reduce possible chromatographic interferences from endogenous compounds.

The utilization of LC-MS/MS bioanalytical methods to quantify domperidone frequently employed has distinctive advantagesin enhancing specificity, sensitivity, and throughput [68,69]. Although the MS detection method eliminates the requirements of complex sample preparation procedures, it has limitations, including relatively expensive equipment and the possibility of matrix effects in biological samples [70]. More to the point, recently the UV detection method, although inexpensive, has been generally replaced by LC-MS/MS since it requires high analyte concentrations which is often impractical when biological sample volumes are limited. [71].

Based on the existing methods for quantifying domperidone, LC coupled with MS detector exhibit rapid, more sensitive, and more selective analysis than UV and fluorescence-based chromatographic techniques. UPLC-MS/MS has demonstrated to be the best method, requiring a small amount of plasma sample compared to LC coupled with UV or fluorescence detection, it exhibits enhanced sensitivity, specificity, and overall reliability [60–62]. In addition, UPLC-MS/MS methods employ simple sample pretreatment procedures [60,62].

Sensitivity is crucial due to the low Cmax of domperidone, which ranges from approximately 20 to 102 ng/mL depending on the dosage form. It is important that analytical method of choice is capable to capture all relevant pharmacokinetic data, particularly at the tail end of the curve. This ensures not only scientific accuracy but also supports informed clinical decision-making.

In addition, in the context of pharmacokinetic-based formulation development for domperidone, selecting sensitive and validated analytical methods is essential for comparing various formulations. Such methods allow for precise quantification of plasma concentrations at different time points, which is vital for characterizing absorption profiles and determining bioavailability. The ability to accurately detect low concentrations is particularly important for distinguishing the performance of different formulations. Consequently, the choice of analytical method directly influences the reliability of pharmacokinetic data, which in turn supports formulation optimization and dosage-making decisions in clinical pharmacotherapy.

Finally, for future work, it is important to note that among the studies discussed, there is still lack of studies focused on the similtaneous analysis of domperidone and its metabolites. Developing analytical methods capable to quantify domperidone, alongside with its metabolites in plasma, would help to understand domperidone's disposition. The challenges for such analysis lie to the physicochemical features and similar structures of domperidone and its metabolites, so their separation demands the optimization of the analytical conditions to get a satisfactory resolution [39,74]. Such methods could also estimate potential drug-drug interactions, in particular for co-administered drugs with similar metabolic pathways, thereby contributing to ensure drug safety [72,73].

Although many studies have reported simultaneous analysis of several specific drugs, there is still much research to be done in this field, in order to develop a better understanding of the effect of pharmacokinetics in patients who receive multiple regimens during therapy. Such research would also support the development

of fixed-dose combination formulation for use bioavailability and bioequivalence studies, while it would reduce the overall cost of analysis

4. Conclusion

This concise review delineated the use of HPLC and UPLC, referred to as liquid chromatography (LC), coupled with different detection modes, including mass spectrometry, UV, and fluorescence, for quantification of domperidone in plasma or serum matrix. LC-MS/MS is the most selected analytical method for quantifying domperidone in the matrix. It offers better sensitivity, provides rich information from MS data, and allows for a shorter time analysis. The acidic condition using formic acid of the mobile phase and ESI in positive ion modes is the most often used to analyze domperidone in LC-MS. Based on the sensitivity of the method, the MS detector is more beneficial. Among the existing methods, a UPLC-MS/MS method could be the best method for facilitating the analysis of many samples in a very short period of time, and only a small amount of plasma sample is needed.

This review provides an overview for the researchers before developing a newly quantification method, in particular regarding the sample extraction or detection method for future work. However, there is still a limitation in the study to simultaneously quantifying domperidone and its metabolites and other co-administered drugs, which may affect the pharmacokinetics. The development of simultaneous multi-drug measurement methods, not much reported, would sipport bioavailability and bioequivalence studies of fixed-dose combination formulations, as well as clinical studies to understand drug-drug interaction. Hence, future studies could be directed toward developing new methods that incorporate appropriate clean-up procedures or optimized chromatographic conditions, and compare their ability and efficiency to separate domperidone together with other target analytes.

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Conflict Of Interest

The authors have no conflict of interest.

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