

Review Article

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Determination of montelukast and non-sedating antihistamine combination in pharmaceutical dosage forms: A review

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Abstract: Combining non-sedating antihistamines (NSAs) with montelukast (MON) has been found to significantly enhance the therapeutic efficacy against daytime and composite nasal symptoms, including rhinorrhea, sneezing, and itching. This article reviews the current analytical methods employed for the identification and quantitative determination of MON in combination with NSAs in various marketed formulations. The most commonly used methods for the determination of MON and NSAs in combination are chromatographic methods (high-performance liquid chromatography [HPLC] and thin-layer chromatography) and spectrometry methods (spectrofluorometry and spectrophotometry). Recent preferences in the analysis of MON and NSAs in combination samples prove the primacy of HPLC (61%) and confirm the general trends moving toward more sensitive methods, with a higher resolution potential, consumption of small quantities of samples and reagents, and requiring less analysis time.

Keywords: non-sedating antihistamines, montelukast, analysis, review

1 Introduction

Montelukast (MON) is 2-[1-[(1*R*)-1-[3-[(1*E*)-2-(7-chloroquinolin-2-yl)ethenyl]phenyl]-3-[2-(2-hydroxypropan-2-yl)phenyl]propyl]sulfanylmethyl]cyclopropyl]acetic acid. It is a selective leukotriene receptor antagonist which is used in the management of chronic asthma, treatment of allergic rhinitis, and as a prophylactic for exercise-induced asthma [1].

Second-generation non-sedating H1-antihistamines, like cetirizine (CET), ebastine (EBA), bilastine (BIL), rupatadine (RUP), and loratadine (LOR), and third-generation H1-antihistamines, like levocetirizine (LEV), fexofenadine (FEX), and desloratadine (DES), demonstrate a greater affinity for peripheral H1 receptors over central nervous system H1 receptors and cholinergic receptors. This selectivity reduces the likelihood of adverse effects, such as sedation, while effectively treating allergic symptoms. Their peripheral selectivity stems from their zwitterionic nature at physiological pH, making them highly polar and unable to penetrate the blood–brain barrier, thereby minimizing sedation.

Non-sedating antihistamines (NSAs) show promise in managing allergic rhinitis by alleviating symptoms like nasal itching, sneezing, and rhinorrhea. They are also effective in treating acute and chronic urticaria [2]. Combining NSAs with MON has been found to significantly enhance the therapeutic efficacy against daytime and composite nasal symptoms, including rhinorrhea, sneezing, and itching [3–5].

Structurally, all non-sedating H1-antihistamines have a piperidine nucleus except for CET and LEV, which are diaryl-substituted piperazines [3,6].

MON, when combined with NSAs, presents a unique analytical challenge due to the diverse chemical structures and physicochemical properties of NSA compounds. As a result, a wide range of analytical techniques have been developed and reported for their analysis, including high-performance liquid chromatography (HPLC), thin-layer chromatography (TLC), and various spectrophotometric methods.

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Although combinations of NSAs with MON are of significant importance, a comprehensive review encompassing all the analytical techniques used for their determination has yet to be published. This article seeks to fill that gap by presenting a detailed overview of the analytical methods employed to determine these combinations in pharmaceutical preparations. Along with a general overview of the techniques, this article also provides an in-depth examination of published studies on the analysis of each specific combination. It consolidates references from 2001 onward, obtained by searching the most comprehensive scientific databases: Science Direct, Springer Link, PubMed, Scopus, and Google Scholar; the search particularly focused on recent methodologies for analyzing these combinations across various pharmaceutical matrices.

2 Spectrophotometric methods

Various spectrophotometric methods such as first-order derivative [7–12], second-order derivative [13], and ratio derivative spectrophotometry [13–15] have been reported for the analysis of MON and LEV combination. Among them, Choudhari *et al.* [11] presented data, indicating that their method is the most sensitive, achieving the lowest limit of quantitation (LOQ) values (0.090 and $0.178 \mu\text{g}\cdot\text{mL}^{-1}$ for MON and LEV, respectively) compared to other derivative methods. The methods proposed by Patel *et al.* and Sankar *et al.* [7,12] were tested on bulk and laboratory mixtures, as well as on dosage form samples; however, they were not properly validated, so their reliability cannot be assured. Additionally, three absorption correction methods [10–12] have been reported for the determination of this combination. Sankar *et al.* [12] did not provide the limits of detection (LODs) and LOQs for their method, while the method proposed by Manisaikumar *et al.* [10] demonstrated greater sensitivity than that of Choudhari *et al.* [11], with LODs of 0.0528 and $0.4130 \mu\text{g}\cdot\text{mL}^{-1}$ for LEV and MON, respectively. Other spectrophotometric techniques, including simultaneous equation [9,16], area under the curve [17], dual wavelength [13], and bivariate calibration [13], have also been proposed, all with quantitation limits sufficiently sensitive and appropriate for determining these drugs in bulk and pharmaceutical preparations.

The combination of MON with FEX has been analyzed using first-order derivative spectrophotometry [18] and the simultaneous equation method [19,20]. Although LOD values were not reported in the studies of Sowjanya and Sastri [19], the available data suggest that the first-order derivative method [18] appears to be more sensitive than the simultaneous equation methods.

The first-order derivative spectrophotometric [21] and Q-ratio methods [22] have been reported for determining the RUP and MON combination. While no definitive conclusions can be drawn about the sensitivity of these two methods due to the absence of LOD values in the study of Rupali *et al.* [22], the linear ranges presented are comparable and appropriate for spectrophotometric analysis.

Two simultaneous equation methods [23,24], an absorption correction method [25], and a second-derivative spectrophotometric method [26] were reported for the determination of BIL and MON combination, the second derivative method [26] demonstrating greater sensitivity than the methods reported in Kolekar *et al.* and Patel *et al.* [23,24], with LOD values of 0.1216 and $0.3686 \mu\text{g}\cdot\text{mL}^{-1}$ for MON and BIL, respectively.

One article per combination dealing with spectrophotometric methods employing second derivative, ratio derivative, and first derivative techniques has been reported for the combination of LOR [27], DES [28], and [DES] with MON.

It is worth mentioning that methanol has been commonly used as a solvent in many of these methods, which undermines their green and environmentally friendly status due to methanol's toxicity and harmful environmental impact.

The experimental conditions and technical details of these methods are summarized in Table 1.

3 Spectrofluorometric methods

A limited number of spectrofluorometric methods have been reported for the analysis of MON with NSA combinations.

A spectrofluorometric method was also developed with excitation and emission wavelengths of 261 and 287 nm for FEX and 392 and 487 nm for MON, respectively. The calibration curves were found to be linear over concentration ranges of 20 – $100 \mu\text{g}\cdot\text{mL}^{-1}$ for FEX and 2 – $10 \mu\text{g}\cdot\text{mL}^{-1}$ for MON. The LODs were determined to be $0.36 \mu\text{g}\cdot\text{mL}^{-1}$ for FEX and $0.73 \mu\text{g}\cdot\text{mL}^{-1}$ for MON [30].

Abdel Hamid *et al.* [31] introduced an eco-friendly synchronous fluorescence spectrofluorimetric method for the simultaneous analysis of MON and FEX. This method measures the relative synchronous fluorescence intensity of both drugs in methanol, with a $\Delta\lambda$ of 60 nm, using wavelengths of 405 nm for MON and 288 nm for FEX. The method demonstrated linearity in the ranges of 0.1 – $2.0 \mu\text{g}\cdot\text{mL}^{-1}$ for MON and 2.0 – $20.0 \mu\text{g}\cdot\text{mL}^{-1}$ for FEX. The LODs were 0.018 and $0.441 \mu\text{g}\cdot\text{mL}^{-1}$ for MON and FEX, respectively.

The method of Prajapati *et al.* [30] appears to be more sensitive than that of Abdel Hamid *et al.* [31] with LODs of 0.018 and $0.441 \mu\text{g}\cdot\text{mL}^{-1}$ for MON and FEX, respectively.

Table 1: Spectrophotometric methods used for the analysis of MON and NSA combination

No.	MON+	Matrix	Technique	Wavelength (nm)	Solvent	LOD ($\mu\text{g}\cdot\text{mL}^{-1}$)	Linear range ($\mu\text{g}\cdot\text{mL}^{-1}$)	Ref.
1	LOR	Tablets	Second derivative	MON, 359.7; LOR, 276.1	Acetonitrile–water (80:20 (v/v))	NA	MON, 4.4–22.1; LOR, 6.4–32.1	[27]
2	DES	Tablets	Ratio first derivative	MON, 218.6; DES, 262.0	Methanol	MON, 0.17; DES, 0.72	5–40 for both	[28]
3	CET	Tablets	First derivative	MON, 335; CET, 217	Methanol	CET, 0.112; MON, 0.010	MON, 6–28; CET, 2–20	[29]
4	LEV	Bulk and tablets	First derivative	MON, 350.2; LEV, 211.8	0.5% w/v aqueous sodium lauryl sulfate	MON, 0.993; LEV, 0.361	3–30 for both	[7]
5	LEV	Tablets	Ratio first derivative	MON, 250.4; LEV, 238.4	—	MON, 0.090; LEV, 0.277	MON, 4–12; LEV, 2–6	[14]
6	FEX	Bulk and tablets	Simultaneous equation	MON, 344.5; FEX, 259	0.1 N NaOH	NA	MON, 1–35; FEX, 50–180	[19]
7	RUP	Tablets	Q-ratio	260 isobestic; RUP, 240	Methanol	NA	4–24 for both	[22]
8	LEV	Tablets	First derivative	MON, 291.60; LEV, 238.20	0.1 N NaOH	LEV, 1.05; MON, 3.69	MON, 10–60; LEV, 5–30	[8]
9	RUP	Tablets	First derivative	MON, 273.4; RUP, 297.2	Methanol	RUP, 0.76; MON, 0.36	5–25 for both	[21]
10	LEV	Bulk and tablets	Ratio first derivative	MON, 281; LEV, 240	Methanol	LEV, 0.2979; MON, 0.3178	MON, 3–30; LEV, 2–32	[15]
11	FEX	Tablets	First derivative	MON, 340; FEX, 212.6	Acetonitrile–buffer–methanol, 50:30:20 (% v/v)	MON, 0.312; FEX, 0.512	4–24 for both	[18]
12	*LEV	Tablets	Simultaneous equation	–250.14, 284.79, and 231.27	Methanol	MON, 0.28; LEV, 0.52	MON, 6–18; LEV, 3–12	[9]
			First derivative	ABP, 275.15; MON, 296.26; LEV, 246.61		MON, 0.25; LEV, 0.46		
13	BIL	Tablets	Second derivative	MON, 326.4; BIL, 226.8	Methanol	MON, 0.1216; BIL, 0.3686	MON, 2–14; BIL, 4–28	[26]
14	**LEV	Bulk and capsules	First derivative	MON, 256.5; LEV, 248; AMB, 256.5	Methanol	LEV, 0.4483; MON, 0.6961	MON, 2–12; LEV; AMB, 10–70	[10]
			Absorbance correction	345, 230, and 307		LEV, 0.05280; MON, 0.4130		
15	BIL	Tablets	Simultaneous equation	274.5 and 351.5	50% alcohol	BIL, 0.7253; MON, 0.6726	MON, 1–20; BIL, 1–32	[23]
16	BIL	Tablets	Simultaneous equation	282 and 344	Methanol	MON, 0.21; BIL, 0.44	MON, 2–12; BIL, 4–24	[24]
17	BIL	Tablets	Absorbance correction	252 and 344	Methanol	MON, 0.21; BIL, 0.43	MON, 2–12; BIL, 4–24	[25]
18	LEV	Tablets	First derivative	MON, 340; LEV, 331	Methanol	MON, 0.09; LEV, 0.178	MON, 4–12; LEV, 2–6	[11]
			Absorption factor	232 and 279		MON, 0.107; LEV, 0.124		

(Continued)

Table 1: Continued

No.	MON+	Matrix	Technique	Wavelength (nm)	Solvent	LOD ($\mu\text{g}\cdot\text{mL}^{-1}$)	Linear range ($\mu\text{g}\cdot\text{mL}^{-1}$)	Ref.
19	FEX	Bulk and tablets	Simultaneous equation	259.60 and 283	Methanol	FEX, 5.94; MON, 2.023	MON, 6–20; FEX, 30–120	[20]
20	LEV	Tablets	Absorbance correction	287 and 232	Methanol	NA	MON, 2–40; LEV, 1–40	[12]
21	LEV	Tablets	Multiwavelength First derivative	232.2 and 229				
			Area under the curve	MON, 231.1; LEV, 216.5 MON, 263.6–293.6; LEV, 222–242	Methanol	MON, 1.06; LEV, 1.23	5–30 for both	[17]
22	LEV	Tablets	Bivariate calibration	220 and 230	Methanol	LEV, 0.261; MON, 0.079	4–28 for both	[13]
			Dual wavelength	MON, 355 and 390; LEV, 208 and 214.4		LEV, 0.374; MON, 0.273		
			Second derivative	MON, 293.2; LEV, 244		LEV, 1.177; MON, 0.785		
			Ratio difference	MON, 296.4 and 344.2; LEV, 216 and 232		LEV, 0.229; MON, 0.352		
23	LEV	Bulk and tablets	Simultaneous equation	229 and 284	Methanol	MON, 1.1; LEV, 0.7	MON, 4–20; LEV, 2–10	[16]
24	BIL	Tablets	Extraction method	BIL, 211; MON, 365		BIL, 0.23; MON, 0.45	BIL, 2–12; MON, 6–14	[30]
			First-order derivative	MON, 211; BIL, 365		BIL, 0.12; MON, 1.18	BIL, 1–5; MON, 10–30	
			Simultaneous equation	BIL, 272; MON, 285; BIL, 211		MON, 0.4; BIL, 1.23	BIL, 10–50; MON, 6–14	
			Q-absorption ratio	215 Isosbestic; BIL, 211		BIL, 1.18; MON, 0.39	BIL, 1–5; MON, 10–30	
			Divisor ratio derivative	MON, 365		BIL, 0.13; MON, 1.12	BIL, 1–5; MON, 10–30	

*+ Acebrophylline (ABP); ***+ ambroxol (AMB); NA: not reported.

Derayea et al. [32] developed a spectrofluorometric method for estimating MON and BIL in pharmaceutical dosage forms by utilizing the synchronized fluorescence amplitude at the first derivative's peaks, specifically at 381 nm for MON and 324 nm for BIL. Calibration plots showed excellent linearity over concentration ranges of 50–2,000 ng·mL⁻¹ for MON and 50–1,000 ng·mL⁻¹ for BIL. The method's development included careful optimization of experimental conditions, such as selecting the optimal $\Delta\lambda$, choice of the solvent, the effect of diluting solvents, buffers, pH modifiers, and the impact of various organized media like surfactants and macromolecules. This method was found to be highly sensitive, with LOD values of 16.5 ng·mL⁻¹ for MON and 10.9 ng·mL⁻¹ for BIL. The method was found to be comparable in its performance to the spectrophotometric method reported by Prajapati et al. [30].

RUP and MON were quantified spectrofluorometrically by using the first derivative synchronous spectrofluorometric intensities in an aqueous solution containing McIlvaine's buffer at pH 2.60. The intensities were measured at 261 nm for RUP and 371 nm for MON. The method demonstrated linearity within the concentration ranges of 0.10–4.00 µg·mL⁻¹ for RUP and 0.20–1.60 µg·mL⁻¹ for MON [33].

A validated method utilizing second derivative synchronous fluorometry was reported for the simultaneous analysis of DES and MON in their co-formulated tablets. The method involved measuring the synchronous fluorescence intensities of both drugs in McIlvaine's buffer, pH 2.3, in the presence of carboxymethyl cellulose sodium (CMC) as a fluorescence enhancer, with a constant wavelength difference ($\Delta\lambda$) of 160 nm. Peak amplitudes of the second derivative synchronous fluorescence spectra were determined at 288 nm for DES and 385 nm for MON. The method exhibited a linear relationship between the concentration and peak amplitude over the concentration ranges of 0.10–2.00 µg·mL⁻¹ for DES and 0.20–2.00 µg·mL⁻¹ for MON [34].

4 Chromatographic methods

Various chromatographic methods have been described for the determination of MON in combination with NSAs in various marketed formulations. Chromatographic techniques like HPLC, TLC, and ultraperformance liquid chromatography have been used.

4.1 TLC methods

In the last two decades, TLC has become one of the most useful chromatographic methods, especially for qualitative

analysis and preparative separations. Quantitative determination by TLC has never been as popular as gas chromatography and HPLC, due to problems with sample applications, development, and evaluation. However, due to the recent developments in instrumentation for TLC, which will lead to a general improvement in accuracy and precision, it is now increasingly being used for the quantitative determination of drugs in tablets, capsules, solutions, ointments, and many other formulations [35].

Densitometric TLC methods have been developed for the determination of LEV and MON in tablets [8,36–38]. Among literature reports, the method by Smita et al. [37] is the most sensitive, with LOD values of 1.536 µg·mL⁻¹ for MON and 2.864 µg·mL⁻¹ for LEV. Justification for the choice of detection wavelengths was provided for all methods except for those in the studies of Shah et al. and Vekaria et al. [39,40]. All methods were validated for linearity, accuracy, and precision, with the study of Mahmoud et al. [41] additionally claiming their method to be eco-friendly.

The combination of BIL and MON was also analyzed using TLC [39,42,43]. All three methods were validated, with justifications provided for the selection of detection wavelengths. However, only the method of Balar et al. [43] was further demonstrated to be stability-indicating through the analysis of forced degradation samples.

The TLC methods reported for determining the combination of FEX and MON [40,44] demonstrated comparable sensitivity. However, the method of Vekaria et al. [40] did not provide justification for the selection of detection wavelengths.

Table 2 provides an overview of various TLC methods that have been reported in the literature.

4.2 HPLC methods

HPLC is particularly well suited for assessing the purity and quality of pharmaceutical preparations, especially when gas-liquid chromatography (GLC) is unsuitable due to the insufficient thermal stability or low volatility of the components. As a result, HPLC is favored over GLC for product quality control (QC) in most pharmaceutical companies and is included in most international pharmacopeias. The development of highly selective adsorbents and advancements in the sensitivity of flow-through spectrophotometric, fluorometric, and electrochemical detectors have further boosted the use of HPLC in pharmaceutical analysis.

Reversed-phase high-performance liquid chromatography (RP-HPLC) has been widely utilized for quantifying MON in

Table 2: TLC methods used for the analysis of MON and NSA combination

No.	MON+	Matrix	Plate	Mobile phase	Detection λ (nm)	Working range (ng/spot)	LOD (ng/spot)	Ref.
1	LEV	Tablets	Silica gel 60 F ₂₅₄	Ethyl acetate-methanol-triethylamine (5:5:0.02 v/v/v)	240	LEV, 200–600; MON, 400–1,200	20.63 MON, 21.12 LEV	[8]
2	LEV	Tablets	Silica gel 60 F ₂₅₄	Toluene-ethyl acetate-methanol-ammonia (2.5:7.2:5.1 v/v/v/v)	231	LEV, 500–2,500; MON, 1,000–5,000	50.0 MON, 90.0 LEV	[36]
3	LEV	Tablets	Silica gel 60 F ₂₅₄	Chloroform-methanol-toluene-glacial acetic acid (10:5:3:0.5 v/v/v/v)	269	MON, 200–3,200; LEV, 400–1,300	1.536 MON, 2.864 LEV	[37]
4	LEV	Tablets	Silica gel 60 F ₂₅₄	Acetone-methanol-toluene (2:2:6 v/v/v)	240	LEV, 0–300; MON, 100–600	8.0 LEV, 16.0 MON	[38]
5	BIL	Tablets	Silica gel 60 F ₂₅₄	Ethyl acetate-toluene-methanol-ammonia (7:0.5:1.5:0.5 v/v/v/v)	254	BIL, 800–4,800; MON, 400–2,400	0.235 BIL, 0.362 MON	[42]
6	BIL	Tablets	Silica gel 60 F ₂₅₄	Toluene-Methanol (6:5:3.5 v/v)	243	BIL, 200–1,200; MON, 100–600	NA	[39]
7	BIL	Tablets	Silica gel 60 F ₂₅₄	Chloroform acetonitrile-ethyl acetate-ammonia (4:6:0.1 v/v/v)	282	MON, 100–500; BIL, 200–1,000	26.26 BIL, 33.34 MON	[43]
8	FEX	Tablets	Silica gel 60 F ₂₅₄	Toluene-ethyl acetate-methanol-ammonia (30%) (0.5:7:2:0.5 v/v/v/v)	220	FEX, 2,400–10,800; MON, 200–900	100.0 FEX, 50.0 MON	[44]
9	FEX	Tablets	Silica gel 60 F ₂₅₄	Ethyl acetate-methanol-ammonia (30%) (7:3:0.5 v/v/v)	215	FEX, 9,000–1,800; MON, 150–750	100.6 FEX, 40.0 MON	[40]
10	CET	Tablets	Silica gel 60 F ₂₅₄	Ethyl acetate-methanol-ammonia solution (25%) (14:3:2 v/v/v)	230	CET, 40–2,000; MON, 120–1,000	3.94 CET, 2.08 MON	[45]
11	LOR	Tablets	Silica gel 60 F ₂₅₄	Ethyl acetate-ethanol (9:1 v/v)	260	MON, 300–3,600; LOR, 200–400	27 MON, 7.0 LOR	[41]

NA: not reported.

combination with NSAs in pharmaceutical dosage forms. Most of the reported methods employed isocratic elution using a RP column (C₈ or C₁₈) and mobile phases composed of organic solvent and buffer mixtures adjusted to specific pH levels.

The combination of LEV and MON in tablet formulations has been analyzed using RP chromatographic methods, applying various combinations of stationary and mobile phases [15,36,46–57]. Although all the methods have been validated and proved to meet required standards, the method of Sonawane *et al.* [50] is particularly noteworthy for being stability-indicating as proven to be effective through the analysis of forced degradation samples, suggesting that it can detect even minor amounts of degradation products alongside the intact analyte(s). This implies a potentially lower LOD compared to other methods (0.00028 $\mu\text{g}\cdot\text{mL}^{-1}$ LEV and 0.0032 $\mu\text{g}\cdot\text{mL}^{-1}$ MON, respectively). Erkmen *et al.*'s method [53], on the other hand, was optimized using the one factor at a time (OFAT) approach. This approach involves optimizing individual factors sequentially, which can improve reliability, but it may not necessarily achieve the same low LOD as a method specifically designed to be stability-indicating like the method of Sonawane *et al.* [50]. Nonetheless, since the method of Erkmen *et al.* [53] has been validated, its sensitivity is adequate for its intended application, although it may not reach the smallest LOD compared to the method in Sonawane *et al.* [50]. In conclusion, while both methods are validated and effective within their specific contexts, the method of Sonawane *et al.* [50] likely offers greater sensitivity (smaller LOD) and more robust linear range, particularly due to its stability-indicating nature, which has been validated through forced degradation studies.

Comparing the HPLC methods used for the determination of RUP and MON combination in bulk and tablets [58–62], the method proposed by Sutar and Magdum [60] demonstrated superior sensitivity with a lower LOD and a broader linear range compared to other methods, which, while validated and within acceptable ranges, exhibited slightly narrower linear ranges. The use of central composite design in optimizing the method of Sutar and Magdum [60] significantly enhanced its reliability. It is important to highlight that all methods underwent rigorous validation to ensure their reliability, sensitivity, and accuracy. However, only methods of Sutar and Magdum and Jani *et al.* [60,62] were specifically proven to be stability-indicating, a crucial feature for evaluating the stability of the analyte under varying conditions.

The HPLC methods for determining the BIL and MON combination in bulk and tablet forms [63–70] were all rigorously validated, among which methods reported in the studies of Tiruveedhi *et al.*, Vijayalakshmi *et al.*, Swathi *et al.*, Sunkara and Ajitha, and Roshdy *et al.* [63–65,68,69]

were additionally proven to be stability-indicating. Notably, the method developed by Vijayalakshmi et al. [64] was the most sensitive, with LOD values of $0.018 \mu\text{g}\cdot\text{mL}^{-1}$ for BIL and $0.024 \mu\text{g}\cdot\text{mL}^{-1}$ for MON. Of these methods, the one by Roshdy et al. [69] stands out as the only method that was eco-friendly, stability-indicating, and systematically optimized using an experimental design approach.

Upon comparing the reported methods for the determination of DES and MON combination in the tablet form [71–73], the method of Gandhi et al. [73] showed the lowest sensitivity, with the lowest LOD values (0.176 and $0.087 \mu\text{g}\cdot\text{mL}^{-1}$ for DES and MON, respectively) among the three methods with acceptable linear ranges for routine analysis, substantiating its ability to detect low concentrations of the analytes, while the method of Mistry et al. [71] exhibited the lowest sensitivity among the three methods, with the highest LOD values (11.51 and $4.06 \mu\text{g}\cdot\text{mL}^{-1}$ for MON and DES, respectively), making it particularly ineffective in detecting very low concentrations of the analytes which contradicts its claimed stability-indicating capability and inconsistent with its broad linear range. On the other hand, the method of Mallesham et al. [72] demonstrated moderate sensitivity, with a slightly higher LOD than that reported by Gandhi et al. [73], making it less sensitive but still effective for most analytical purposes.

Numerous methods have been reported for the determination of FEX and MON in pharmaceutical dosage forms [74–89]. The low LOD is crucial for detecting trace amounts of analytes, and among the methods reported, the most sensitive LODs for FEX and MON were found in methods of Chabukswar et al. and Godavarthi et al. [87,88]. The LOD for FEX reported in Chabukswar et al. [87] is $0.028 \mu\text{g}\cdot\text{mL}^{-1}$, and for MON in Godavarthi et al. [88] the LOD is $0.02 \mu\text{g}\cdot\text{mL}^{-1}$, making them particularly sensitive for both analytes. High LOD methods such as those reported in Tamilselvi and Sruthi and Mohite et al. [75,79], with LODs of $3.83 \mu\text{g}\cdot\text{mL}^{-1}$ for FEX and $2.96 \mu\text{g}\cdot\text{mL}^{-1}$ for MON, respectively, indicate a less sensitive approach, which might be less suitable for samples where the analytes are present in very low concentrations. Wide linear range is desirable for quantifying a broad spectrum of concentrations without requiring dilution or concentration of samples. The method described by Godavarthi et al. [88] stands out with linear ranges of $12\text{--}144 \mu\text{g}\cdot\text{mL}^{-1}$ for FEX and $0.05\text{--}10 \mu\text{g}\cdot\text{mL}^{-1}$ for MON, which allows it to handle diverse sample concentrations effectively. A narrow linear range is observed in the study of Padmavaathi and Subba Rao [83] for FEX ($10\text{--}30 \mu\text{g}\cdot\text{mL}^{-1}$) and the study of Uthirapathy et al. [85] for MON ($0.4\text{--}2.4 \mu\text{g}\cdot\text{mL}^{-1}$). These narrower ranges may limit the applicability of the method to samples with specific concentration levels, requiring additional steps to fit into the detectable range.

Most methods maintain a flow rate of $1.0 \text{ mL}\cdot\text{min}^{-1}$, which is optimal for standard HPLC systems and ensures a balance between the analysis time and resolution. Exceptions, like the method in Manasa et al. [84] with a flow rate of $0.8 \text{ mL}\cdot\text{min}^{-1}$, may be adjusted for specific analytical needs but could require recalibration of equipment. The widespread use of C_{18} columns across methods highlights their versatility and compatibility with various mobile phases. The occasional use of C_8 columns (as in the study of Uthirapathy et al. [85]) may be due to specific interaction requirements, but generally C_{18} is preferred for its broad applicability.

The method described in Chabukswar et al. [87] offers the best balance between sensitivity (LOD of $0.028 \mu\text{g}\cdot\text{mL}^{-1}$ for FEX), linear range ($0.6\text{--}120 \mu\text{g}\cdot\text{mL}^{-1}$ for FEX), and practicality (standard flow rate and use of C_{18} column). It is highly sensitive, covers a wide concentration range, and remains practical for routine analysis. For applications requiring the detection of very low concentrations, the method of Godavarthi et al. [88] with its low LOD for MON ($0.02 \mu\text{g}\cdot\text{mL}^{-1}$) would be the preferred choice, although it may require more complex mobile phase preparation.

This comparative analysis highlights the trade-offs between sensitivity, linear range, and practical simplicity, enabling the selection of the most appropriate method based on specific analytical needs.

Many methods have been reported for the analysis of EBA and MON in pharmaceutical preparations [90–96], and these methods vary in levels of control parameters (column type, mobile phase composition, mobile phase flow rate, and wavelength of detection), which are consequently affect the method outputs (detection limit, linear range, and practicality of use). Low LOD values are essential for detecting small quantities of analytes. Among the methods compared, the most sensitive method for MON is found in the study of Ghode et al. [96], with an LOD of $0.041 \mu\text{g}\cdot\text{mL}^{-1}$, and for EBA the same method reports an LOD of $0.0211 \mu\text{g}\cdot\text{mL}^{-1}$. This method stands out for its ability to detect very low concentrations, making it ideal for samples where the analytes might be present in trace amounts.

Higher LODs are seen in methods like Shrikrishna and Nisharani [91], with LODs of $1.05 \mu\text{g}\cdot\text{mL}^{-1}$ for MON and $1.13 \mu\text{g}\cdot\text{mL}^{-1}$ for EBA, which indicate a lower sensitivity. These methods may not be as effective in detecting small quantities and might be better suited for samples with higher analyte concentrations. The method of Shireesha et al. [94] covers broad linear ranges from 0 to $16 \mu\text{g}\cdot\text{mL}^{-1}$ for MON and $0\text{--}35 \mu\text{g}\cdot\text{mL}^{-1}$ for EBA. These ranges are advantageous for quantifying varying concentrations without the need to alter the method significantly. Some methods, such as those reported in the study of Shrikrishna and Nisharani

Table 3: HPLC methods used for the analysis of MON and NSA combination

No.	MON+	Matrix	Column	Mobile phase	Detection λ (nm)	Working range ($\mu\text{g}\cdot\text{mL}^{-1}$)	LOD ($\mu\text{g}\cdot\text{mL}^{-1}$)	Ref.
1	LEV	Tablets	Phenyl, 50 mm $\times$ 2.1 mm, 40°C	Solvent A: KH_2PO_4 buffer, pH 6.5; solvent B: acetonitrile; gradient from 45% B to 70% B in 2 min, at a flow rate of $0.4\text{ mL}\cdot\text{min}^{-1}$	231	LEV, 12.5–75; MON, 25–150	NA	[46]
2	LEV	Tablets	C_{18} , 250 $\times$ 4.6 mm, 5 μm	Na_2HPO_4 buffer (0.02 M)–methanol (25:75 v/v), pH adjusted to 7 with orthophosphoric acid, at a flow rate of $1.0\text{ mL}\cdot\text{min}^{-1}$	231	LEV, 1–10; MON, 2–20	0.5 LEV, 0.2 MON	[36]
3	LEV	Tablets	C_8 , 150 $\times$ 4.6 mm, 5 μm	KH_2PO_4 (0.02 M)–methanol (40:60 v/v, pH 5.0), at a flow rate of $1.0\text{ mL}\cdot\text{min}^{-1}$	218	LEV, 5–20; MON, 10–40	2.493 LEV, 0.489 MON	[47]
4	LEV	Tablets	C_8 , 250 $\times$ 4.6 mm, 5 μm , 35°C	KH_2PO_4 buffer (0.05 M, pH 7.5)–methanol, 20: 80 v/v, at a flow rate of $1.2\text{ mL}\cdot\text{min}^{-1}$	225	LEV, 10–260; MON, 10–350	2.26 LEV, 2.41 MON	[48]
5	LEV	Tablets	C_{18} , 250 $\times$ 4.6 mm, 5 μm , 30°C	Ammonium acetate buffer (pH 3.5)–methanol (15:85 v/v%), at a flow rate of $1.0\text{ mL}\cdot\text{min}^{-1}$	230	LEV, 3–12; MON, 6–18	0.28 MON, 0.52 LEV	[49]
6	LEV in tablets	Tablets	C_{18} , 250 $\times$ 4.6 mm, 5 μm , 30°C	Acetonitrile–phosphate buffer, pH 7.0 (60:40), at a flow rate of $1.0\text{ mL}\cdot\text{min}^{-1}$	230	LEV, 12.56–37.68; MON, 23.73–71.2	0.079 LEV, 0.156 MON	[50]
7	LEV	Tablets	C_8 , 250 $\times$ 4.6 mm, 5 μm	Acetonitrile–0.5% triethylamine in water (90:10 v/v), pH adjusted to 5.5, at a flow rate of $0.8\text{ mL}\cdot\text{min}^{-1}$	231	LEV, 2–32; MON, 3–30	0.00028 LEV, 0.0032 MON	[15]
8	LEV	Tablets	C_{18} , 150 $\times$ 4.6 mm, 5 μm	10 mM acetonitrile–ammonium acetate (65:35% v/v and pH 4.2), at a flow rate of $1.0\text{ mL}\cdot\text{min}^{-1}$	230	LEV, 25–75; MON, 50–150	0.05 LEV, 0.1 MON	[51]
9	LEV	Tablets	C_{18} , 250 $\times$ 4.6 mm, 5 μm	Methanol and sodium hydrogen phosphate and orthophosphoric acid buffer (pH 7.0) in the ratio of 75:25 v/v, at a flow rate of $1.2\text{ mL}\cdot\text{min}^{-1}$	230	MON, 8–28; LEV, 4–14	0.0173 LEV, 0.056 MON	[52]
10	LEV	Tablets	C_{18} , 150 $\times$ 4.6 mm, 5 μm , 40°C	Methanol–10 mM ammonium acetate buffer (85:15 v/v), pH 4.0, at a flow rate of $1\text{ mL}\cdot\text{min}^{-1}$	240	0.5–100 for both	0.16 LEV, 0.05 MON	[53]
11	LEV	Tablets	C_{18} , 100 $\times$ 4.6 mm, 5 μm , 25°C	Buffer (2.8 g L^{-1} Na_2HPO_4 , pH 7.0)–acetonitrile (90:10 v/v) at a flow rate of $1.0\text{ mL}\cdot\text{min}^{-1}$	230	5–100 for both	NA	[54]
12	LEV	Tablets	C_{18} , 250 $\times$ 4.6 mm, 5 μm	Acetonitrile–methanol–water (40:40:20 v/v), at a flow rate of $1.0\text{ mL}\cdot\text{min}^{-1}$	232	30–60 for both	NA	[55]
13	LEV	Tablets	C_{18} , 150 $\times$ 4.6 mm, 5 μm , 40°C	Methanol–water (75:25 v/v), at a flow rate of $1.0\text{ mL}\cdot\text{min}^{-1}$	235	LEV, 50–150; MON, 100–300	0.42 LEV, 0.16 MON	[56]
14	LEV	Tablets	C_{18} , 250 $\times$ 4.6 mm, 5 μm , 30°C	Buffer (pH 3.6)–acetonitrile (35:65 v/v), at a flow rate of $1.0\text{ mL}\cdot\text{min}^{-1}$	231	LEV, 12.5–75; MON, 25–150	0.04 MON, 0.08 LEV	[57]
15	RUP	Bulk and tablets	C_8 , 250 $\times$ 4.6 mm, 5 μm , 40°C	Methanol–acetonitrile–buffer (40:30:30 v/v), (pH 3 adjusted with H_3PO_4), at a flow rate of $1.0\text{ mL}\cdot\text{min}^{-1}$	270	5–15 for both	NA	[58]
16	RUP	Tablets	C_8 , 150 $\times$ 4.6 mm, 5 μm	Acetonitrile–phosphate buffer, pH 4.7 (60:40, v/v) at a flow rate of $1.2\text{ mL}\cdot\text{min}^{-1}$	254	100–300 for both	NA	[59]
17	RUP	Tablets	C_{18} , 150 $\times$ 4.6 mm, 5 μm	Acetonitrile–phosphate buffer (75:25 v/v), pH adjusted to 4.0, at a flow rate of $1\text{ mL}\cdot\text{min}^{-1}$	226	100–300 $\mu\text{g}\cdot\text{mL}^{-1}$ for both	4.06 MON, 4.10 LEV	[60]
18	RUP	Bulk and tablets	C_8 , 250 $\times$ 4.6 mm, 5 μm	Methanol–acetonitrile–buffer, 40:30:30 v/v, pH 3.2 at a flow rate of $1.0\text{ mL}\cdot\text{min}^{-1}$	270	10–80 for both	0.141 RUP, 0.167 MON	[61]
19	RUP	Bulk and tablets	C_{18} , 250 $\times$ 4.6 mm, 5 μm	Methanol–water (90:10 v/v) with 0.1% triethylamine, pH 3.41 at a flow rate of $1\text{ mL}\cdot\text{min}^{-1}$	260	15–40 $\mu\text{g}\cdot\text{mL}^{-1}$ for both	1.49 RUP, 1.21 MON	[62]

(Continued)

Table 3: Continued

No.	MON+	Matrix	Column	Mobile phase	Detection λ (nm)	Working range ($\mu\text{g}\cdot\text{mL}^{-1}$)	LOD ($\mu\text{g}\cdot\text{mL}^{-1}$)	Ref.
20	BIL	Bulk and tablets	C ₁₈ , 250 × 4.6 mm, 5 μm	0.1 M Na ₂ HPO ₄ buffer (pH 5.8)–methanol, 55:45 v/v, at a flow rate of 1.0 mL·min ⁻¹	223	BIL, 5–40; MON, 2.5–20	0.133 MON 0.287 BIL	[63]
21	BIL	Bulk and tablets	C ₁₈ , 250 × 4.6 mm, 5 μm	0.1 M KH ₂ PO ₄ (pH 4.2)–methanol (60:40, v/v) at a flow rate of 1.0 mL·min ⁻¹	232	BIL, 10–30; MON, 5–15	0.018 BIL, 0.024 MON	[64]
22	BIL	Bulk and tablets	C ₁₈ , 150 × 4.6 mm, 5 μm , 30°C	0.01 M KH ₂ PO ₄ –methanol (70:30) at a flow rate of 1.0 mL·min ⁻¹	218	BIL, 5–30; MON, 2.5–15	0.32 BIL, 0.24 MON	[65]
23	BIL	Bulk and tablets	C ₁₈ , 150 × 4.6 mm, 5 μm	Methanol and acetonitrile (70:30), pH 3, at a flow rate 1.0 mL·min ⁻¹	260	BIL, 25–150; MON, 5–30	3.99 BIL, 0.98 MON	[66]
24	BIL	Bulk and tablets	C ₁₈ , 250 × 4.6 mm, 5 μm , 25°C	Acetonitrile–Na ₂ HPO ₄ buffer (pH 6.8) 60:40 v/v, at a flow rate of 0.6 mL·min ⁻¹	254	BIL, 160–260; MON, 80–130	7.43 BIL, 3.06 MON	[67]
25	BIL tablets	Tablets	C ₁₈ , 250 × 4.6 mm, 5 μm , 30°C	0.01 M ammonium acetate–acetonitrile, 70:30 v/v, at a flow rate of 1.0 mL·min ⁻¹	220	BIL, 15–30; MON, 2.5–15	0.31 BIL, 0.09 MON	[68]
26	BIL	Tablets	C ₁₈ , 150 × 4.6 mm, 5 μm	Methanol–acetonitrile–phosphate buffer (92:6:2 v/v/v), adjusted to pH 3 with 0.1 (v/v) triethylamine, at a flow rate of 0.8 mL·min ⁻¹	220	BIL, 1.0–50.0; MON, 3.0–40.0	0.28 BIL, 0.96 MON	[69]
27	BIL	Tablets	C ₁₈ , 150 × 4.6 mm, 5 μm	Phosphate buffer (pH 4.5) and acetonitrile in the ratio of 30:70 v/v, at a flow rate of 0.8 mL·min ⁻¹	225	10–50 for both	NA	[70]
28	DES	Tablets	C ₁₈ , 250 × 4.6 mm, 5 μm	0.3% TFA with water–acetonitrile (20:80 v/v), at a flow rate of 1.0 mL·min ⁻¹	230	DES, 40–60; MON, 80–120	11.51 MON, 4.06 DES	[71]
29	DES	Bulk and tablets	C ₈ , 250 × 4.6 mm, 5 μm	K ₂ HPO ₄ buffer (pH: 8.6) and methanol (60:40% v/v), at a flow rate of 0.8 mL·min ⁻¹	261	50–150 for both	2.759 DES, 2.909 MON	[72]
30	DES	Tablets	C ₁₈ , 250 × 4.6 mm, 5 μm	Orthophosphoric acid and water in the ratio of 20:80 v/v, at a flow rate of 1.0 mL·min ⁻¹	280	MON, 10–30; DES, 5–15	0.176 MON, 0.087 DES	[73]
31	FEX	Tablets	C ₁₈ , 250 × 4.6 mm, 5 μm	Methanol–ammonium formate, pH adjusted to 6 with orthophosphoric acid (70:30), at a flow rate of 1.0 mL·min ⁻¹	268	MON, 2–15; FEX, 30–180	0.30 MON 0.36 FEX	[74]
32	FEX	Tablets	C ₁₈ , 250 × 4.6 mm, 5 μm	0.5% orthophosphoric acid (pH 6.0 with trimethylamine)–acetonitrile, 40:60 v/v, at a flow rate of 1.0 mL·min ⁻¹	240	FEX, 72–120; MON, 6–10	3.83 FEX, 0.21 MON	[75]
33	FEX	Tablets	C ₁₈ , 250 × 4.6 mm, 5 μm	Methanol–0.1% orthophosphoric acid (90:10 v/v), pH 6.8, at a flow rate of 1.0 mL·min ⁻¹	226	FEX, 24–120; MON, 2–10	0.036 MON 0.283 FEX	[76]
34	FEX	Tablets	C ₁₈ , 50 × 4.6 mm, 3 μm	Acetonitrile–20 mM KH ₂ PO ₄ , 80:30 (v/v), pH 5.5, at a flow rate of 1.0 mL·min ⁻¹	230	FEX, 80–120; MON, 96–144	0.17 FEX, 0.142 MON	[77]
35	FEX	Tablets	C ₁₈ , 250 × 4.6 mm, 5 μm	Buffer (K ₂ HPO ₄ , 0.02 M, pH 6.0) and methanol (25:75 v/v), at a flow rate of 1.0 mL·min ⁻¹	220	FEX, 84–156; MON, 7–13	0.29 FEX, 0.16 MON	[78]
35	FEX	Tablets	C ₁₈ , 250 × 4.6 mm, 5 μm	Acetonitrile–phosphate buffer (pH 2.8) in the ratio of 70:30 v/v, at a flow rate of 1.0 mL·min ⁻¹	245	FEX, 10–50; MON, 4–20	2.96 MON 2.78 FEX	[79]
36	FEX	Tablets	C ₁₈ , 250 × 4.6 mm, 5 μm , 40°C	Acetonitrile–methanol–50 mM sodium acetate buffer (pH 8.2), 35:40:25 v/v/v, at a flow rate of 1.0 mL·min ⁻¹	210	MON, 12.5–37.5; FEX, 150–450	0.2931 MON, 3.007 FEX	[80]
37	FEX	Tablets	C ₁₈ , 250 × 4.6 mm, 5 μm , 28°C	Orthophosphoric acid (pH 6.2)–methanol (40:60 v/v) at a flow rate of 1.0 mL·min ⁻¹ ; detection λ : 290 nm	290	FEX, 24–72; MON, 2–6	0.139 FEX, 0.140 MON	[81]

(Continued)

Table 3: Continued

No.	MON+	Matrix	Column	Mobile phase	Detection λ (nm)	Working range ($\mu\text{g}\cdot\text{mL}^{-1}$)	LOD ($\mu\text{g}\cdot\text{mL}^{-1}$)	Ref.
38	FEX	Tablets	C ₁₈ , 250 × 4.6 mm, 5 μm	Acetonitrile–buffer (10 mM KH ₂ PO ₄ solution)–methanol, 50:30:20 v/v/v, pH 4.5; at a flow rate of 1.5 mL·min ⁻¹	248	FEX, 20–100; MON, 16–64	0.04 MON 0.07 FEX	[82]
39	FEX	Tablets	C ₁₈ , 150 × 4.6 mm, 5 μm	Buffer (2.72 g·L ⁻¹ KH ₂ PO ₄ –acetonitrile–methanol–water, 44:44:12 v/v, pH 4.0)–acetonitrile (60:40 v/v) at a flow rate of 1.0 mL·min ⁻¹	225	FEX 10–30; MON, 5–15	0.1 FEX, 0.025 MON	[83]
40	FEX	Tablets	C ₁₈ , 100 × 4.6 mm, 5 μm	0.1% triethylamine–acetonitrile (30:70) in isocratic mode, at a flow rate of 0.8 mL·min ⁻¹	220	FEX, 35–105; MON, 2.9–8.7	NA	[84]
41	FEX	Tablets	C ₈ , 150 × 4.6 mm, 5 μm	0.05 M KH ₂ PO ₄ –acetonitrile in the ratio of 35:65, pH 6, adjusted with triethylamine, at a flow rate of 1.0 mL·min ⁻¹	226	FEX, 4.8–28.8; MON 0.4–2.4	NA	[85]
42	FEX	Tablets	C ₈ , 250 × 4.6 mm, 5 μm	Methanol–acetonitrile–1% TFA (80:10:10 v/v/v) at a flow rate of 1.0 mL·min ⁻¹	210	FEX, 30–180; MON, 2.5–15	NA	[86]
43	FEX	Tablets	C ₁₈ , 250 × 4.6 mm, 5 μm , 50°C	Acetonitrile–methanol–water (44:44:12 v/v) pH 3, adjusted with orthophosphoric acid, at a flow rate of 1.0 mL·min ⁻¹	241	FEX, 0.6–120; MON, 0.05–10	0.094 MON, 0.028 FEX	[87]
44	FEX	Tablets	C ₁₈ , 250 × 4.6 mm, 5 μm	Acetonitrile–triethylamine (pH 6) (80:20 v/v), at a flow rate of 1.0 mL·min ⁻¹	220	FEX, 12–144; MON, 1–12	1.41 FEX, 0.02 MON	[88]
45	FEX	Tablets	C ₁₈ , 150 × 4.6 mm, 5 μm	0.1 M KH ₂ PO ₄ buffer (pH 5.0) and methanol in the ratio of 60:40 v/v, at a flow rate of 1.0 mL·min ⁻¹	220	FEX 10–100; MON, 5–15	0.1 MON, 1.0 FEX	[89]
47	EBA	Tablets	C ₁₈ , 150 × 4.6 mm, 5 μm	Methanol–acetonitrile–ammonium acetate (80:10:10, % v/v/v), pH 5.5, adjusted using glacial acetic acid, at a flow rate of 1.2 mL·min ⁻¹	244	10–60 for both	0.819 MON, 0.667 EBA	[90]
48	EBA	Tablets	C ₁₈ , 250 × 4.6 mm, 5 μm	Methanol and water (80:20), pH 3.0 adjusted with orthophosphoric acid at a flow rate of 1.0 mL·min ⁻¹	268	5–25 for both	1.05 MON, 1.13 EBA	[91]
49	EBA	Tablets	C ₁₈ , 150 × 4.6 mm, 5 μm	Methanol and 0.02 M ammonium acetate buffer (pH 5.5, adjusted with dilute acetic acid) in the ratio of 80:20 v/v at a flow rate of 0.8 mL·min ⁻¹	241	2.5–25 for both	0.298 MON, 0.594 EBA	[92]
50	EBA	Tablets	C ₁₈ , 250 × 4.6 mm, 5 μm	Ammonium acetate buffer, acetonitrile, and methanol in a 12:55:33 v/v/v at a flow rate of 1.0 mL·min ⁻¹	250	16–24 for both	0.607 for both	[93]
51	EBA	Tablets	C ₁₈ , 250 × 4.6 mm, 5 μm	Acetonitrile–phosphate buffer, 75:25 v/v (pH 3.0) at a flow rate of 1.0 mL·min ⁻¹	255	MON, 0–16; EBA 0–35	0.607 MON, 0.451 EBA	[94]
52	EBA	Tablets	C ₁₈ , 250 × 4.6 mm, 5 μm	Methanol, acetonitrile, and 0.02 M ammonium acetate buffer (pH 5.5, adjusted with dilute acetic acid) in the ratio of 80:15:05 v/v/v at a mobile phase flow rate of 1.0 mL·min ⁻¹	244	10–50 for both	0.169 MON, 0.195 EBA	[95]
53	EBA	Tablets	C ₈ , 250 × 4.6 mm, 5 μm	Water (pH 2.8, adjusted with TFA) in the composition of 84:16 v/v at a flow rate of 1 mL·min ⁻¹	254	5–60 for both	0.041 MON 0.0211 EBA	[96]
54	RUP + DES FEX	Tablets	CN, 250 × 4.6 mm, 5 μm	Ethanol–water (50:50 v/v, containing 0.04% triethylamine, and pH 4.5) at a flow rate of 0.85 mL·min ⁻¹	220	RUP, DES, and MON, 1–10; FEX, 1–24	0.26 RUP, 0.30 DES, 0.27 FEX, 0.15 MON	[97]
55	LOR	Tablets	C ₁₈ , 250 × 4.6 mm, 5 μm	Buffer (0.025 M sodium dihydrogen phosphate, pH adjusted to 3.7 using dilute orthophosphoric acid)–acetonitrile, 20:80 v/v at a flow rate of 1.0 mL·min ⁻¹	225	MON, 100–600; LOR, 116–580	NA	[27]

[91], offer a more limited range ($5\text{--}25\text{ }\mu\text{g}\cdot\text{mL}^{-1}$ for both analytes), which could restrict their application to specific concentration levels, possibly requiring dilution or concentration steps for certain samples.

The majority of methods maintain a standard flow rate of $1.0\text{ mL}\cdot\text{min}^{-1}$, which is optimal for many HPLC systems, ensuring consistency in retention times and peak resolution. An exception is the method of Leelavathy and Shaheedha [93], which uses a slightly lower flow rate of $0.8\text{ mL}\cdot\text{min}^{-1}$. While this adjustment may help in certain separations, it could also necessitate the recalibration of equipment and adjustment of method parameters.

Most methods utilize C18 columns, known for their versatility and compatibility with a wide range of mobile phases. The method of Ghode et al. [96], however, uses a C_8 column with water and trifluoroacetic acid (TFA), offering a different separation mechanism that may be beneficial in specific scenarios but could require optimization and validation for broader use.

The method of Shrikrishna and Nisharani [91], which uses methanol and water with pH adjustment, stands out for its simplicity. Simple mobile phases reduce the preparation time, minimize the risk of errors, and are easier to replicate, making them ideal for routine analysis, while methods like those in the study of Ghode et al. [96] involve water and TFA, which, while potentially offering better resolution, require careful pH control and preparation, increasing the complexity of the method and the possibility of variability between runs.

The method of Ghode et al. [96] offers the best sensitivity with low LOD values ($0.041\text{ }\mu\text{g}\cdot\text{mL}^{-1}$ for MON and $0.0211\text{ }\mu\text{g}\cdot\text{mL}^{-1}$ for EBA) and an adequate linear range ($5\text{--}60\text{ }\mu\text{g}\cdot\text{mL}^{-1}$ for both analytes). It may be more complex due to the use of TFA and the C_8 column but is highly effective for detecting low analyte concentrations.

This analysis highlights the importance of balancing the sensitivity, linear range, and simplicity when selecting an HPLC method, depending on the specific needs of the analysis.

Several methods have been confirmed as stability-indicating through the analysis of forced degradation samples [50,60,62–65,68,69,71,74,76,77,81,83,90,93]. However, many of the reported methods skipped proper development or optimization, instead incorrectly treating initial adjustments of method control parameters for preliminary separation as method optimization. Only two methods have been optimized using either the OFAT approach [53,69] and another two using the experimental design approach [63,92]. In reality, true optimization should follow the method development stage in the analytical method lifecycle. Even though these methods are fully validated according to the global

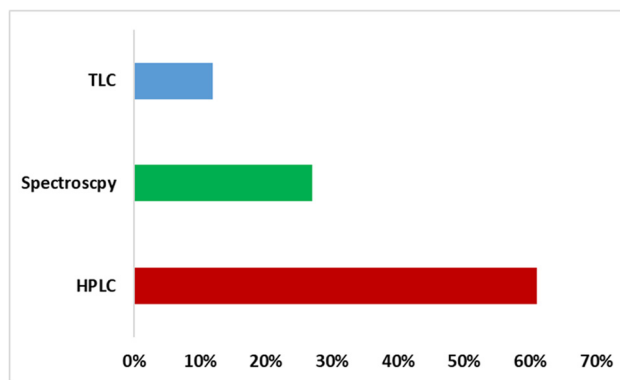


Figure 1: Graph displaying the % ratio of the analytical methods used for the simultaneous estimation of MON and NSA combination.

guidelines on method validation (ICH Q2 (R1)) [58] before being implemented or used routinely, they often fail to demonstrate robustness during routine QC testing and are found to be unsuitable for their intended purpose [59]. Given the strict regulatory requirements and the increasing emphasis on applying quality by design principles in the analytical field (AQbD), it is essential to establish more rigorous standards for publishing analytical methods. This will ensure the development of robust methods that are fit for use in QC laboratories. Notably, no method has been reported to be eco-friendly.

Ghonim et al. [97] developed and validated an eco-friendly RP-HPLC method for the simultaneous determination of MON in combination with RUP, DES, and FEX in a single analytical run. The method was optimized using factorial experimental design and demonstrated adequate sensitivity, with LOD values of $0.26\text{ }\mu\text{g}\cdot\text{mL}^{-1}$ for RUP, $0.30\text{ }\mu\text{g}\cdot\text{mL}^{-1}$ for DES, and $0.27\text{ }\mu\text{g}\cdot\text{mL}^{-1}$ for FEX. Description of the reported HPLC methods is given in Table 3.

5 Conclusions

In recent years, various analytical methods have been reported for the quantitative estimation of drugs in combined pharmaceutical dosage forms. This article summarizes the reported analytical methods for the simultaneous estimation of MON and NSAs in bulk and combined pharmaceutical formulations.

It has been observed that the application of experimental design approaches for the method optimization is limited, which indicates that there is potential for enhancing method optimization. Statistical tools and experimental designs can aid in identifying optimal separation conditions and improving the robustness of analytical

methods. It is noteworthy that although most reported methods are validated according to international guidelines, some may not be suitable for routine QC testing due to their lack of robustness. This underscores the need for more stringent standards in the publication of analytical methods.

This review revealed that RP-HPLC is the most frequently used method (61%), compared to different spectroscopic methods (27%) and TLC methods ($\approx 12\%$). An overview of all the reported analytical methods used for the simultaneous estimation of MON and NSAs in bulk and combined pharmaceutical formulations is presented in Figure 1.

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Data availability statement: The datasets generated during and/or analyzed during the current study are available from the corresponding author on reasonable request.

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